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(54) Title: METASTIN DERIVATIVES AND USE THEREOF

(57) **Abstract:** The invention provides stable metastin derivatives having excellent biological activities (a cancer metastasis suppressing activity, a cancer growth suppressing activity, etc.). By modifying the constituent amino acids of metastin with specific modifying groups, metastin derivatives having more improved blood stability, etc. than native metastin and showing excellent cancer metastasis suppressing activity or cancer growth suppressing activity have been found. Furthermore, it has been found that these metastin derivatives exhibit effects of suppressing gonadotropic hormone secretion, suppressing sex hormone secretion, etc., which are wholly different from the effects heretofore known.

DESCRIPTION

METASTIN DERIVATIVES AND USE THEREOF

TECHNICAL FIELD

The present invention relates to metastin derivatives and use thereof.

BACKGROUND ART

Human-derived metastin (also termed KiSS-1 peptide) (WO 00/24890) and rat or mouse-derived metastin (WO 01/75104) are known. Also, sustained released preparations containing metastin are known (WO 02/85399).

Reportedly, metastin has an effect of suppressing cancer metastasis and is therefore effective for preventing or treating cancers (for example, lung cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, renal cancer, bladder cancer, brain tumor, etc.); metastin also has an effect of controlling pancreatic function and is effective for preventing or treating pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.); and metastin further has an effect of controlling placental function and is effective for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or abnormal delivery (WO 00/24890; WO 01/75104; WO 02/85399).

DISCLOSURE OF THE INVENTION

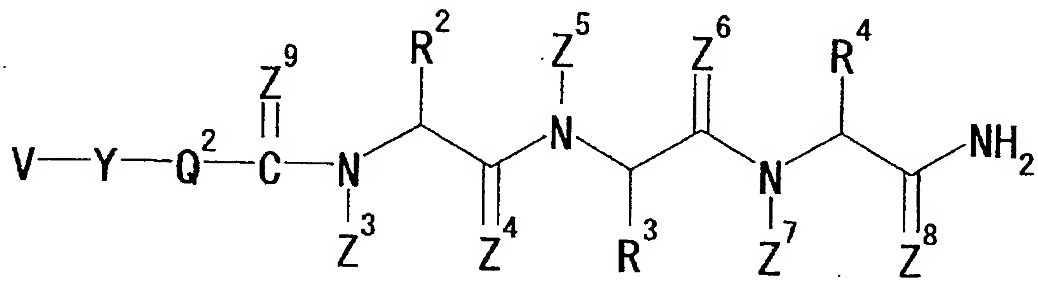
The present invention aims at providing stable metastin derivatives having excellent biological activities (a cancer metastasis suppressing activity, a cancer growth suppressing activity, etc.).

The present inventors have made extensive studies to solve the foregoing problems and as a result, have found that by modifying the amino acids, which constitute metastin, with a specific modifying group, unexpectedly metastin derivative show improved blood stability, etc. as compared to native metastin and further exhibit an excellent cancer metastasis suppressing activity or a cancer growth suppressing activity. The present inventors have further found that unexpectedly these metastin derivatives have an effect of suppressing gonadotropic hormone secretion, an effect of suppressing sex hormone secretion, etc., which are totally different from the effects known so far. Based on these findings, the present inventors have continued further

investigations and come to accomplish the present invention.

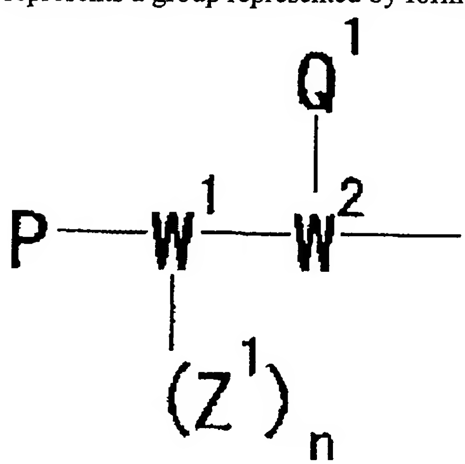
That is, the present invention provides the following features and so on.

(1) A metastin derivative (II) represented by formula:

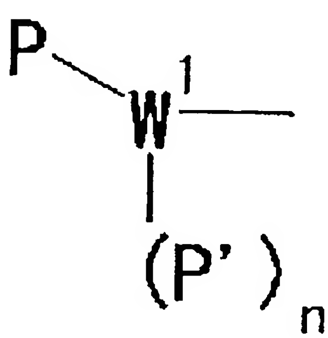


[wherein;

V represents a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that when W^1 is N or CH, n represents 1 and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the

group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

$J^1\text{-}J^2\text{-}C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})\text{-}$

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may

optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

$J^1\text{-}J^2\text{-}C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(wherein:

J^1 and J^2, each has the same significance as described above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as described above;

Z^{10} has the same significance as described above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-

(wherein:

J^1 and J^2 have the same significance as described above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as described above;

Z^{10} has the same significance as described above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein;

J^1 and J^2 have the same significance as described above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as described above; and,

J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

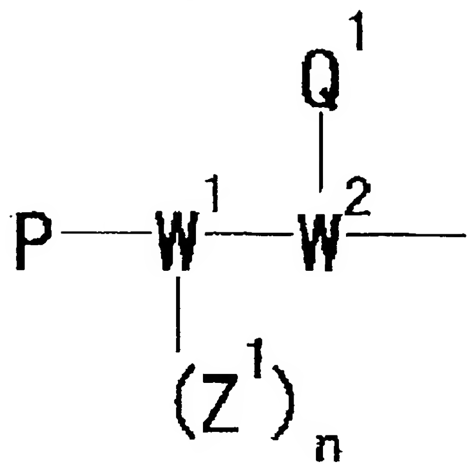
(7) a group represented by formula:

J^1-

(wherein:

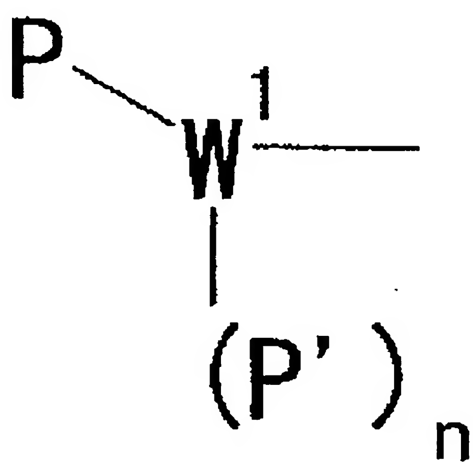
J^1 has the same significance as described above)] (provided that a peptide consisting of the amino acid sequence of 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54, 45-54, 46-54, 47-54, 48-54 or 49-54 in the amino acid sequence represented by SEQ ID NO: 1 is excluded), or a salt thereof.

(2) The metastin derivative (II) according to (1), wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in (1)), or a salt thereof.

(3) The metastin derivative (II) according to (1), wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in (1)), or a salt thereof.

The present invention further provides the following features, and so on.

(4) A prodrug of the metastin derivative (II) according to (1) or a salt thereof.

(5) A pharmaceutical comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(6) The pharmaceutical according to (5), which is an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

(7) The pharmaceutical according to (5), which is an agent for preventing or treating

cancer.

(8) The pharmaceutical according to (5), which is an agent for controlling pancreatic function.

(9) The pharmaceutical according to (5), which is an agent for preventing or treating acute or chronic pancreatitis or pancreatic cancer.

(10) The pharmaceutical according to (5), which is an agent for controlling placental function.

(11) The pharmaceutical according to (5), which is an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

(12) The pharmaceutical according to (5), which is an agent for improving gonadal function.

(13) The pharmaceutical according to (5), which is an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

(14) The pharmaceutical according to (5), which is an agent for inducing or stimulating ovulation.

(15) The pharmaceutical according to (5), which is a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

(16) The pharmaceutical according to (5), which is an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

(17) A method for suppressing cancer metastasis or cancer growth, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(18) A method for preventing or treating cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(19) A method for controlling pancreatic function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(20) A method for preventing or treating acute or chronic pancreatitis or pancreatic cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(21) A method for controlling placental function, which comprises administering to a

mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(22) A method for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(23) A method for improving gonadal function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(24) A method for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(25) A method for inducing or stimulating ovulation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(26) A method for promoting gonadotropic hormone secretion or promoting sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(27) A method for preventing or treating Alzheimer's disease or moderate cognitive impairment, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(28) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

(29) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating cancer.

(30) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for controlling pancreatic function.

(31) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating acute or chronic pancreatitis or pancreatic cancer.

(32) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for controlling placental function.

(33) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

(34) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for improving gonadal function.

(35) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

(36) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for inducing or stimulating ovulation.

(37) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

(38) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

(39) A pancreatic glucagon secretagogue agent comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(40) An agent for promoting urine formation comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(41) An agent for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, comprising the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(42) A method for promoting pancreatic glucagon secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(43) A method for promoting urine formation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(44) A method for preventing or treating obesity, hyperlipemia, type II diabetes

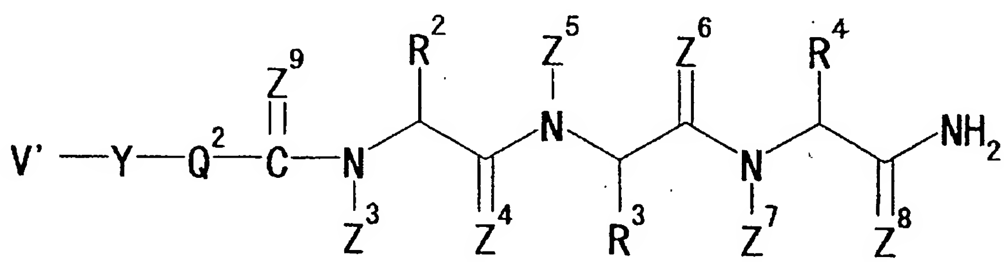
mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof.

(45) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture a pancreatic glucagon secretagogue agent.

(46) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for promoting urine formation.

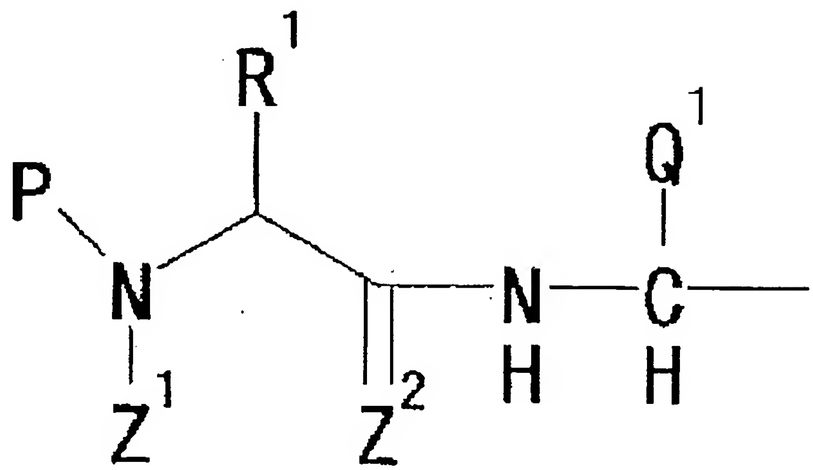
(47) Use of the metastin derivative (II) according to (1) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

(48) An agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion comprising the metastin derivative (III) represented by formula:

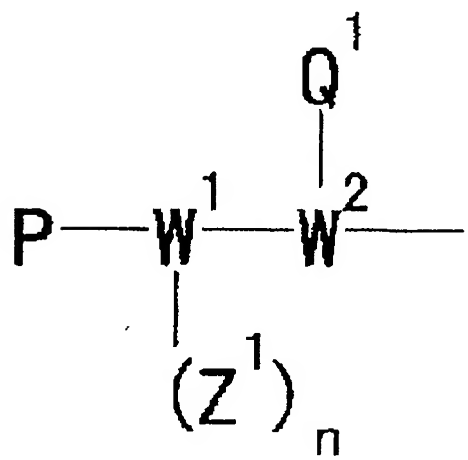


[wherein:

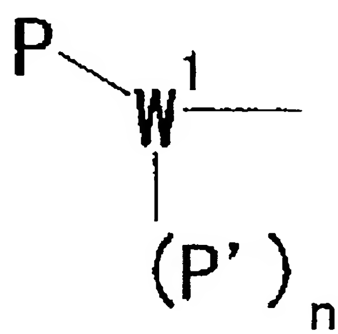
V' represents a group represented by formula:



a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having

carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O; Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent

containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

$J^1\text{-}J^2\text{-}C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(wherein:

J^1 and J^2, each has the same significance as described above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as described above;

Z^{10} has the same significance as described above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-

(wherein:

J^1 and J^2 have the same significance as described above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as described above;

Z^{10} has the same significance as described above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein;

J^1 and J^2 have the same significance as described above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as described above; and

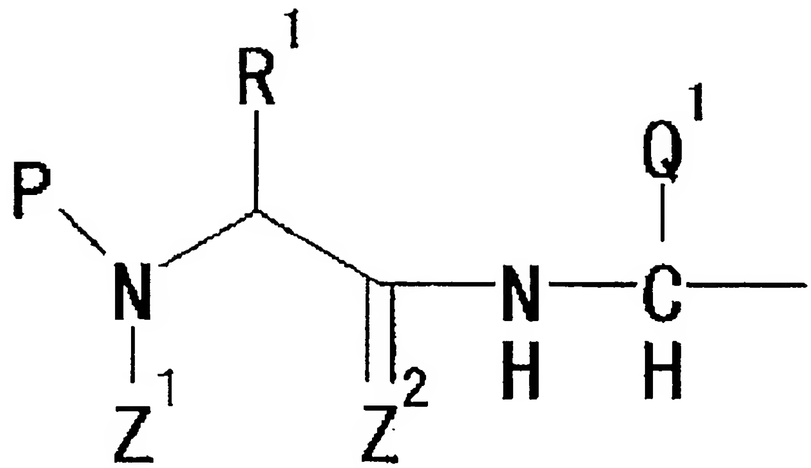
J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

J^1- (wherein J^1 has the same significance as described above)] or a salt thereof, or a prodrug thereof.

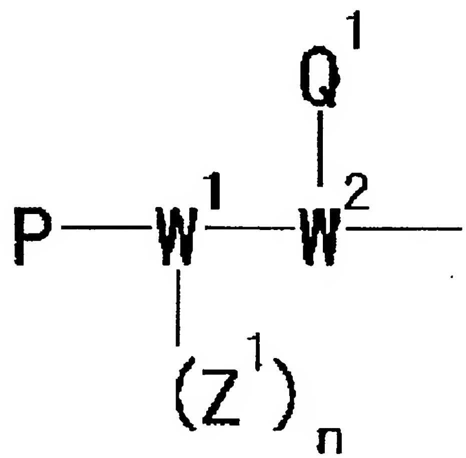
(49) The agent according to (48), wherein the metastin derivative (III) is the metastin derivative (II) according to (1).

(50) The agent according to (48), wherein V' is a group represented by formula:



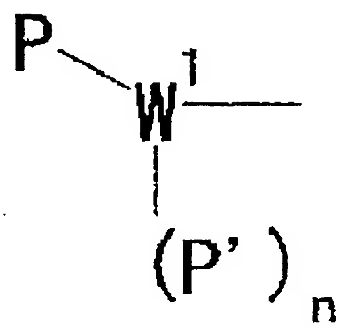
(wherein each symbol has the same significance as described in (48)).

(51) The agent according to (48), wherein V' is a group represented by formula:



(wherein each symbol has the same significance as described in (48)).

(52) The agent according to (48), wherein V' is a group represented by formula:



(wherein each symbol has the same significance as described in claim 48).

(53) The agent according to (48), wherein the metastin derivative (III) is:

(1) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 141),

(2) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 174),

(3) 3-(3-Indolyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 260),

(4) 3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 269),

(5) 2-(indol-3-yl)ethylcarbamoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 279),

(6) D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 286),

(7) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 296),

(8)TyrΨ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 300),

(9) D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 303),

(10) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 305),

(11) D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F) -NH_2 (Compound No. 318),

(12) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 319),

(13) 3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound

No. 322),

(14) 4-Imidazoleacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 323),

(15) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 332),

(16) GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 333),

(17) GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 334),

(18) 3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 339),

(19) Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 341),

(20) Indole-3-acetyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 345),

(21) Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 346),

(22) Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 353),

(23) 3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 354),

(24) Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 358),

(25) 2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 364),

(26) 2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 369),

(27) (2S)-2-acethoxy-3-phenylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 373),

(28) (2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 379),

(29) (2S)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 380),

(30) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),

(31) 3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 386),

(32) Dibenzylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 393),

(33) Benzylphenethylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 417),

(34) Benzoyl-PheΨ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 423),

(35) Benzoyl-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 431),

(36) 3-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 432),

(37) 2-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 435),

(38) 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 436),

(39) Propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 437),
(40) Isobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 438),
(41) Cyclohexanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 439),
(42) Phenylacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 440),
(43) Benzoyl-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 441),
(44) 6-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 445),
(45) Pyrazinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 446),
(46) Cyclopropanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 447),
(47) Trifluoroacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 448),
(48) Benzoyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 449),
(49) Cyclopropanecarbonyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 451),
(50) (R)-3-hydroxy-2-methylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 452),
(51) 2-Hydroxyisobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 453),
(52) 3-Furancarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 454),
(53) Pyrrole-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 455),
(54) 4-Imidazolecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 459),
(55) 6-Hydroxynicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 462),
(56) 6-Chloronicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 463),
(57) 6-(Trifluoromethyl)nicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 464),
(58) Dimethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 467),
(59) 1-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 468),
(60) 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 471),
(61) 4-Aminobenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 472),
(62) 4-Aminomethylbenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 473),
(63) Pyrrole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 474),
(64) Pyrimidine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 475),
(65) Pyrimidine-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 479),
(66) Pyridazine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 480),
(67) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2 (Compound No. 481),
(68) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2 (Compound No. 487),
(69) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2 (Compound No. 488),

(70) D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 490),

(71) D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 491),

(72) D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 492),

(73) D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 493),

(74) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 496),

(75) D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2 (Compound No. 497),

(76) D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 498),

(77) 3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 499),

(78) 3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 500),

(79) D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),

(80) D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 502),

(81) D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 503),

(82)6-Aminocaproyl-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 504),

(83) 3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 505),

(84) 3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 506),

(85) 3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 507),

(86) 3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 508),

(87) Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),

(88)Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 510),

(89) D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 511),

(90) D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),

(91) D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 513),

(92) D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 514),

(93) D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 515),

(94) des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10 (Compound No. 516),

(95) des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 517),

(96)des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10 (Compound No. 518),

(97) des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 519),

(98) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10 (Compound No. 521),

(99) des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 522),

(100) des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 523),

(101) des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 524),

(102) des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 527),

(103) des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 528),

(104) des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 529),

(105) des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 530),

(106) des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 531),

(107) des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 532),

(108) des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 533),

(109) des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 534),

(110) des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 535),

(111) [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 536),

(112) Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 537),

(113) Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 538),

(114) des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 539),

(115) des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 540),

(116) D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 541),

(117) D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 542),

(118) des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 545),

(119) des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 546),

(120) des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 547),

(121) des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10 (Compound No. 548),

(122) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 550),

(123) Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 551),

(124) D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 552),

(125) D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 553),

(126) D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 554),

(127) D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 555),

(128) D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 556),

(129) D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 557),

(130) des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 558),

(131) des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 559),

(132) D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 561),

(133) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 562),

(134) des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 563),

(135) des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 564),

(136) des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 565),

(137) des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 566),

(138) des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 567),

(139) Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 568),

(140) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH2NH,Arg(Me)9,Trp10]MS10 (Compound No. 569),

(141) des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 570),

(142) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 571),

(143) des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 572),

(144) des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 573),

(145) des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 576),

(146) des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 577),

(147) des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 578),

(148) des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 579),

(149) des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 580),

(150) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 584),

(151) des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 585),

(152) des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 586),

(153) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10 (Compound No. 589),

(154) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10 (Compound No. 590),

(155) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10 (Compound No. 591),

(156) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10 (Compound No. 592),

(157) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10 (Compound No. 594),

(158) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10 (Compound No. 595),

(159) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10 (Compound No. 596),

(160) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 597),

(161) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10 (Compound No. 598),

(162) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10 (Compound No. 599),

(163) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10 (Compound No. 600),

(164) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10 (Compound No. 601),

(165) des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 Compound No. 602),

(166) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 603),

(167) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10 (Compound No. 604),

(168) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10 (Compound No. 605),

(169) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10 (Compound No. 607),

(170) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10 (Compound No. 608),

(171) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10 (Compound No. 609),

(172) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10 (Compound No. 610),

(173) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 611),

(174) des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 612),

(175) des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 613),

(176) des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 614),

(177) des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 615),

(178) des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 616),

(179) des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 617),

(180) des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 618),

(181) des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 619),

(182) des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 620),

(183) des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 621)

(184) des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 622),

(185) des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 623),

(186) des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 624),

(187) des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 625),

(188) des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 626),

(189) des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 627),

(190) des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 628),

(191) des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 629),

(192) des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 630),

(193) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 631),

(194) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 632),

(195) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 633),

(196) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 634),

(197) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 635),

(198) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,NMePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

(Compound No. 636),

(199) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 637),

(200) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 638),

(201) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10 (Compound No. 639),

(202) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10 (Compound No. 641),

(203) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10 (Compound No. 642),

(204) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10 (Compound No. 643),

(205) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10 (Compound No. 644),

(206) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10 (Compound No. 645),

(207) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10 (Compound No. 646),

(208) des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 647),

(209) [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 648),

(210) Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 649),

(211) [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 650),

(212) Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 651),

(213) pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 652),

(214) des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 653),

(215) des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound

No. 654),

(216) des(1)-Ac-[D-Tyr2,D-Trp3,NMeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 655),

(217) des(1)-Ac-[D-Tyr2,D-Trp3,NMeSer5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 656),

(218) des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 657),

(219) des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 658),

(220) des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 659),

(221) des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 660),

(222) des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 661),

(223) des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 662),

(224) des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 663),

(225) des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 664),

(226) des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 665),

(227) des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 666),

(228) des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 667),

(229) des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 668),

(230) des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 669),

(231) des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 670),

(232) des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 671),

(233) des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound

No. 672),

(234) des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 674),

(235) [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 675)

(236) Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 676)

(237) Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10 (Compound No. 677)

(238) Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10 (Compound No. 678)

(239) des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 679)

(240) des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (CompoundNo. 680)

(241) des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 681)

(242) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10 (Compound No. 682)

(243) des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 685)

(244) des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 686)

(245) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10 (Compound No. 688)

(246) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10 (CompoundNo. 689)

(247) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 691)

(248) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 692)

(249) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 693)

(250) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 694)

(251) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

(Compound No. 695)
(252) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 696)
(253) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10 (Compound No. 698)
(254) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10 (Compound No. 699)
(255) des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10 (Compound No. 700)
(256) des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10 (CompoundNo. 701)
(257) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 702)
(258) des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 703).

(54) The agent according to (48) to (53), which is a down-regulating agent for gonadotropic hormone or sex hormone.

(55) The agent according to (48) to (53), which is a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

(56) The agent according to (48) to (55), which is an agent for preventing or treating hormone-dependent cancer.

(57) A method for suppressing gonadotropic hormone secretion or suppressing sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (III) according to (48) or a salt thereof, or a prodrug thereof.

(58) A method for down regulating gonadotropic hormone or sex hormone, which comprises administering to a mammal an effective dose of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof.

(59) A method for down regulating human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9, which comprises administering to a mammal an effective dose of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof.

(60) A method for preventing or treating hormone-dependent cancer, which comprises administering to a mammal an effective dose of the metastin derivative according to

(48) or a salt thereof, or a prodrug thereof.

(61) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion.

(62) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for gonadotropic hormone or sex hormone.

(63) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

(64) Use of the metastin derivative according to (48) or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer.

(65) A metastin derivative represented by formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl, cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, 3-(4-Hydroxyphenyl)propionyl, glycyl, tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl;

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm;

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine;

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid;

XX5 represents Ser, Thr or Val;

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4- pyridylalanine or 4-fluorophenylalanine;

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val;

XX9 represents Arg, Orn, Arg(Me) or Arg(symMe2);

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine), or a salt thereof.

(66) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No.

305),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),

Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 516),

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 540),

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 541),

Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 545),

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2(Compound No. 548),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 553),

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 555),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 564),

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 566),

Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 567),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 580),
Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 584),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2 (Compound No. 590),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2 (Compound No. 591),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2 (Compound No. 599),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2 (Compound No. 600),
Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 602),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2 (Compound No. 608),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612)、
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 615),
Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 616),
Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 617),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 621),
Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 623),
Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 625),
Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 626),
Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),
Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 629),
Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 630),
Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 635),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2 (Compound No. 642),

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 648),

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 649),

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 650),

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 651),

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 652),

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 657),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 662),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663),

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 666),

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 667),

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 670),

Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 671),

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 672),

6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 674), or salts thereof.

(67) Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound

No. 552), Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558), 3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559), Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562), Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571), Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579), Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585), Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589), Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592), For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612), Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613), Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618), Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627), Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637), Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638), Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658), Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660), Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663), or salts thereof.

(68) The agent according to (48) above, which is an agent for potentiating immunity (prophylactic agent for infection after bone-marrow transplant, an agent for potentiating immunity intended for cancer).

(69) The agent according to (48) above, which is a prophylactic/therapeutic agent for bulbospinal muscular atrophy.

(70) The agent according to (48) above, which is a prophylactic/therapeutic agent for protecting ovary.

(71) The agent according to (48) above, which is a prophylactic/therapeutic agent for benign prostate hypertrophy (BPH).

(72) The agent according to (48) above, which is a prophylactic/therapeutic agent for gender identity disorder.

(73) The agent according to (48) above, which is a prophylactic/therapeutic agent for in vitro fertilization (IVF).

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows evaluation of the chemotaxis inhibition activity of Compound Nos. 322, 305, 303, 286, 232 and 141 using hOT7T175-expressed CHO cells. On the abscissa, FBS- designates the absence of FBS, FBS+ designates the presence of FBS, 322 designates the addition of Compound No. 322, 305 designates the addition of Compound No. 305, 303 designates the addition of Compound No. 303, 286 designates the addition of Compound No. 286, 232 designates the addition of Compound No. 232, 141 designates the addition of Compound No. 141, (1-54) designates the addition of metastin (1-54), and (45-54) designates the addition of metastin45-54. The ordinate denotes a relative activity when the chemotactic activity in the presence of FBS is made 100%.

FIG. 2 shows evaluation of the tumor growth inhibition activity of Compound No. 322 and Metastin (1-54) using tumor-bearing mice with human colonic carcinoma-derived cell line SW620, wherein the value indicates (mean value) $\pm$ (standard error). Symbols open diamond, open circle, closed circle and closed square designate the results obtained when Vehicle (distilled water), Compound No. 322 (0.1 mM), Compound No. 322 (1 mM), and Metastin (Metastin 1-54) were added, respectively. The abscissa denotes the number of days after injection. The bar on the abscissa designates a dosing period. The ordinate denotes a tumor size (mm^3).

FIG. 3 shows evaluation of the tumor growth inhibition activity of Compound No. 305 and Metastin (1-54) using tumor-bearing mice with human colonic carcinoma-derived cell line SW620, wherein the value indicates (mean value) $\pm$ (standard error). Symbols open diamond, open circle, closed circle and closed square designate the results obtained when Vehicle (distilled water), Compound No. 305 (0.1 mM), Compound No. 305 (1 mM), and Metastin (Metastin 1-54) were added, respectively. The abscissa denotes the number of days after injection. The bar on the

abscissa designates a dosing period. The ordinate denotes a tumor size (mm^3).

FIG. 4 shows the results obtained by monitoring changes in blood glucose level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed triangle, closed circle and closed diamond designate blood glucose level in the saline group, the 17 nmol/kg metastin group, the 80 nmol/kg metastin group and the 170 nmol/kg metastin group, respectively. The value indicates (mean $\pm$ SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 5 shows the results obtained by monitoring changes in blood glucagon level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood glucagon level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean $\pm$ SE) (n = 6-9). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 6 shows the results obtained by monitoring changes in blood insulin level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood insulin level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean $\pm$ SE) (n = 6-9).

FIG. 7 shows the results obtained by monitoring changes in blood corticosterone level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood corticosterone level in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean $\pm$ SE) (n = 4-5).

FIG. 8 shows the results obtained by monitoring changes in thyroid hormone (T3) level in blood when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate thyroid hormone (T3) level in blood in the saline group and the 80 nmol/kg metastin group, respectively. The value indicates (mean $\pm$ SE) (n = 4-5).

FIG. 9 shows the results obtained by monitoring changes in blood glucose level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle and closed circle designate blood glucose level in the saline group

and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 6-9). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group

FIG. 10 shows the results obtained by monitoring changes in blood glucose level when a metastin derivative was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed circle and closed triangle designate blood glucose level in the saline group, the 80 nmol/kg KiSS1-305 group and the 80 nmol/kg metastin group, respectively. The value indicates (mean ± SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group and symbol ** designates that the P-value is 0.01 or less, when compared to the saline group.

FIG. 11 shows the results obtained by monitoring changes in blood glucagon level when metastin was intravenously injected into rats under no anesthesia. In the figure, symbols open circle, closed circle and closed triangle designate blood glucagon level in the saline group and the 80 nmol/kg KiSS1-305 (Compound No. 305) group, the 80 nmol/kg KiSS1-322 (Compound No. 322) group, respectively. The value indicates (mean ± SE) (n = 5). Symbol * designates that the P-value is 0.05 or less, when compared to the saline group.

FIG. 12 shows the level of estradiol contained in the rat plasma. In the figure, the ordinate and the abscissa denote the estradiol level and the drug receiving groups, respectively.

FIG. 13 shows the level of progesterone contained in the rat plasma. In the figure, the ordinate and the abscissa denote the estradiol level and the drug receiving groups, respectively.

FIG. 14 shows changes in the blood FSH level in immature rat by metastin injection.

FIG. 15 shows changes in the blood LH level in immature rat by metastin injection.

FIG. 16 shows changes in the blood progesterone level in immature rat by metastin injection.

FIG. 17 shows changes in the blood FSH level in rat by metastin injection.

FIG. 18 shows changes in the blood LH level in rat by metastin injection.

FIG. 19 shows changes in the blood testosterone level in rat by metastin injection.

FIG. 20 shows the number of oocytes per individual rat in each group measured in TEST EXAMPLE 13. In the figure, symbol closed diamond designates data for per individual rat and symbol closed square designates a mean value in each group.

FIG. 21 shows the blood estradiol level in each dosing group measured in TEST EXAMPLE 13. In the figure, symbol closed triangle designates data for per individual rat and symbol closed square designates a mean value in each group.

FIG. 22 shows the blood progesterone level in each group measured in TEST EXAMPLE 13. In the figure, symbol closed triangle designates data for per individual rat and symbol closed square designates a mean value in each group.

BEST MODE OF EMBODIMENTS OF THE INVENTION

In the formulae described above, n represents 0 or 1; W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0); W^2 represents N or CH; Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group; and Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

wherein, when Z^2, Z^4, Z^6 or Z^8 represents hydrogen atom, a structure of the moiety represented by $>C= Z^2$, $>C= Z^4$, $>C= Z^6$ or $>C= Z^8$ each indicates a structure of $>CH_2$.

The C_{1-3} alkyl group used includes methyl group, ethyl group, propyl group and isopropyl group.

W^1 is preferably N and W^2 is preferably CH.

Preferred combinations of Z^1 through Z^8 further include the cases that Z^1 and Z^3 represent hydrogen atom, each of Z^5 and Z^7 represents hydrogen atom or a C_{1-3} alkyl group and each of Z^2, Z^4, Z^6 and Z^8 represents O or S.

More preferably, the combinations of Z^1 through Z^8 include:

(a) the case where Z^1 is hydrogen atom, Z^3 is hydrogen atom, Z^5 is hydrogen atom and Z^7 is hydrogen atom, and Z^2 is O, Z^4 is O, Z^6 is O and Z^8 is O;

(b) the case where Z^1 is hydrogen atom, Z^3 is hydrogen atom, Z^5 is hydrogen atom and Z^7 is hydrogen atom, and Z^2 is O, Z^4 is O, Z^6 is O and Z^8 is S;

(c) the case where Z^1 and Z^3 are hydrogen atom and Z^5 is hydrogen atom, Z^7 is methyl group and Z^2 is O, and Z^4 is O, Z^6 is O and Z^8 is O; etc. Among these cases, (a) and (b) are preferred.

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted

with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group. Inter alia, preferred R^1 includes (1) hydrogen atom or (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, more preferably includes (1) hydrogen atom or (2) a C_{1-8} alkyl group substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group.

The "C_{1-8} alkyl group" used includes, for example, a linear C_{1-8} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc., and a cyclic C_{3-8} alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. C_{1-3} alkyl groups such as methyl, ethyl, etc. are particularly preferred.

The "optionally substituted carbamoyl group" used includes, for example, carbamoyl, a mono-C_{1-6} alkylcarbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), a di-C_{1-6} alkylcarbamoyl group (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), a mono- or di-C_{6-14} arylcarbamoyl group (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- or 7-membered heterocyclic carbamoyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.) and the like.

The "optionally substituted hydroxyl group" used includes, for example, hydroxy group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group, an optionally substituted C_{7-16} aralkyloxy group, etc. The "optionally substituted C_{1-6} alkoxy group," "optionally substituted C_{6-14} aryloxy group" and "optionally substituted C_{7-16} aralkyloxy group" used are those of the "optionally substituted C_{1-6} alkoxy group," "optionally substituted C_{6-14} aryloxy group" and "optionally substituted C_{7-16} aralkyloxy group" in Substituent group A, which will be later described.

The "aromatic cyclic group" in "optionally substituted aromatic cyclic group" includes, for example, an aromatic hydrocarbon group, aromatic heterocyclic group, an aromatic fused cyclic group, an aromatic fused heterocyclic group, etc.

The "aromatic hydrocarbon group" used includes, for example, a C_{6-14} aryl group such as phenyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, cyclooctatetraenyl, etc.

The "aromatic heterocyclic group" used includes, for example, a 5- to 14-membered, preferably 5- to 10-membered, more preferably 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples are thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isooxazolyl (e.g., 3-isooxazolyl), etc.

The "aromatic fused cyclic group" used includes a C_{8-14} aromatic fused cyclic group such as naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl (e.g., 2-anthryl, 9-anthryl) and the like.

The "aromatic fused heterocyclic group" used includes, for example, a 5- to 14-memberd (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms, or a monovalent group formed by removing one optional hydrogen atom from a 7- to 10-membered aromatic bridged-hetero ring in 5- to 14-membered (preferably 5- to 10-membered) ring containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples of these groups used are quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl) and the like.

The "substituent" used for the "aromatic cyclic group" includes a substituent selected from the Substituent group A, which will be later described.

For R^1, there are used hydrogen atom, carbamoylmethyl, 2-carbamoylethyl, hydroxymethyl, 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclohexylmethyl, phenyl, acetoxymethyl, methoxymethyl, etc., preferably, hydroxymethyl, 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 3-indolemethyl, methyl, isobutyl, etc., and more preferably, hydroxymethyl, 1-hydroxyethyl, etc.

R^2 represents (1) hydrogen atom, (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group. Among them, preferred are (1) hydrogen atom, (2) a cyclic or linear C_{1-10} alkyl group, or (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group. In particular, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group is preferred.

The cyclic C_{1-10} alkyl group used includes, for example, a C_{3-8} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

Examples of the linear C_{1-10} alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl, etc.

The C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group used includes, for example, a C_{3-7} cycloalkyl-C_{1-3} alkyl group such as cyclopentylmethyl, cyclohexylmethyl, etc.

Examples of R^2 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclohexylmethyl, benzyl, hydroxymethyl, 2-carbamoylethyl, tert-pentyl, etc.; among them, preferred are methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc., more preferably, propyl, isopropyl, isobutyl, etc.

R^3 represents:

(1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent,

(2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent,

(3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an

additional substituent, or,

(4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent.

The "optionally substituted basic group" used includes, for example, (1) a guanidino group optionally having 1 or 2 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (2) an amino group optionally having 1 to 3 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (3) a C_{1-6} alkylcarbonylamino group (e.g., acetamido) optionally substituted with a guanidino group optionally having 1 or 2 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc., (4) a C_{1-6} alkylcarbonylamino group (e.g., acetamido) optionally substituted with an amino group optionally having 1 to 3 substituents from a C_{1-6} alkyl, a C_{1-6} acyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, acetyl, propionyl, etc.), etc. Among them, preferred are guanidino, N-methylguanidino, N,N-dimethylguanidino, N,N'-dimethylguanidino, N-ethylguanidino, N-acetylguanidino, amino, N-methylamino, N,N-dimethylamino, aminoacetamido, guanidinoacetamido, amidino, etc.

The "additional substituent" other than the "optionally substituted basic group" used includes a substituent selected from the Substituent group A later described.

Examples of the "C_{1-8} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

The "aralkyl group" used includes, for example, a C_{7-16} aralkyl group such as benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl, etc.

The "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" used includes, for example, a C_{3-7} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group of carbon atoms not greater than 7" used includes, for example, a 5- to 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms, etc. Specifically examples used are pyrrolidinyl (e.g.,

1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

Examples of the "C_{1-4} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

For R^3, there are used, for example, (1) 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-propylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 2-(N-methylguanidino)ethyl, 4-aminobutyl, 4-(N-methylamino)butyl, 4-(N,N-dimethylamino)butyl, 3-aminopropyl, 2-aminoethyl, aminomethyl, aminoacetamidomethyl, guanidinoacetamidomethyl, 2-(guanidinocarbonyl)ethyl, (2) 4-guanidinobenzyl, 4-aminobenzyl, (3) 4-guanidinocyclohexylmethyl, 4-aminocyclohexylmethyl, (4) 1-amidinopiperidin-4-ylmethyl, 4-pyridylmethyl, etc., preferably, 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-propylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 2-(N-methylguanidino)ethyl, 4-aminobutyl, 4-(N-methylamino)butyl, 4-(N,N-dimethylamino)butyl, 3-aminopropyl, 2-aminoethyl, 4-aminobenzyl, aminoacetamidomethyl, guanidinoacetamidomethyl, etc., and more preferably, 3-guanidinopropyl, 3-(N-methylguanidino)propyl, 3-(N,N-dimethylguanidino)propyl, 3-(N,N'-dimethylguanidino)propyl, 3-(N-ethylguanidino)propyl, 3-(N-acetylguanidino)propyl, 4-guanidinobutyl, 4-(N-methylguanidino)butyl, 2-guanidinoethyl, 4-aminobutyl, etc.

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group

consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7; and preferably, a C_{1-4} alkyl group substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7; and,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7.

Examples of the "C_{1-4} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{6-12} aromatic hydrocarbon group" used includes, for example, a monocyclic C_{6-12} aromatic hydrocarbon group such as phenyl, cyclooctatetraenyl, etc.

The "5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" used includes, for example, a 5- to 14-membered, preferably 5- to 10-membered, more preferably 5- or 6-membered monocyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms. Specific examples used are thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl),

pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), etc.

The "C_{8-14} aromatic fused cyclic group" used includes, for example, naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl (e.g., 2-anthryl, 9-anthryl), etc.

The "optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" includes, for example, a 5- to 14-memberd (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms, or a monovalent group formed by removing one optional hydrogen atom from a 7- to 10-membered aromatic bridged-hetero ring in 5- to 14-membered (preferably 5- to 10-membered) ring containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples used are quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl), etc.

The "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" used includes, for example, a C_{3-7} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group of carbon atoms not greater than 7" used includes, for example, a 5- or 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms, in addition to 1 to 7 carbon atoms, such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The substituents used for these "C_{6-12} aromatic hydrocarbon group," "5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "C_{8-14} aromatic fused cyclic group," "5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting

of nitrogen, oxygen and sulfur atoms," "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" and "non-aromatic heterocyclic group of carbon atoms not greater than 7" include, for example, substituents selected from oxo, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted C_{6-14} aryl, an optionally substituted C_{7-16} aralkyl, an optionally substituted C_{1-6} alkoxy, hydroxy, an optionally substituted C_{6-14} aryloxy, an optionally substituted C_{7-16} aralkyloxy, mercapto, an optionally substituted C_{1-6} alkylthio, an optionally substituted C_{6-14} arylthio, an optionally substituted C_{7-16} aralkylthio, an optionally substituted amino[amino, an optionally substituted mono- or di-C_{1-6} alkyl-amino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, etc.), an optionally substituted mono- or di-C_{2-6} alkenyl-amino (e.g., vinylamino, propenylamino, isopropenylamino), an optionally substituted C_{2-6} alkynylamino (e.g., 2-butyn-1-yl-amino, 4-pentyn-1-yl-amino, 5-hexyn-1-yl-amino), an optionally substituted mono- or di-C_{3-8} cycloalkyl-amino (e.g., cyclopropylamino, cyclohexylamino), an optionally substituted C_{6-14} arylamino (e.g., phenylamino, diphenyllamino, naphthylamino), an optionally substituted C_{1-6} alkoxyamino (e.g., methoxyamino, ethoxyamino, propoxyamino, isopropoxyamino), formylamino, an optionally substituted C_{1-6} alkylcarbonylamino (e.g., acetylamino, propionylamino, pivaloylamino, etc.), an optionally substituted C_{3-8} cycloalkylcarbonylamino (e.g., cyclopropylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino, etc.), an optionally substituted C_{6-14} aryl-carbonylamino (e.g., benzoylamino, naphthoylamino, etc.), an optionally substituted C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.), an optionally substituted C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), an optionally substituted C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.)], formyl, carboxy, an optionally substituted C_{1-6} alkylcarbonyl (e.g., acetyl, propionyl, pivaloyl, etc.), an optionally substituted C_{3-8} cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 1-methyl-cyclohexyl-carbonyl, etc.), an optionally substituted C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), an optionally substituted C_{7-16} aralkylcarbonyl (e.g., phenylacetyl, 3-phenylpropionyl,

etc.), an optionally substituted 5- to 7-membered heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), an optionally esterified carboxyl, an optionally substituted carbamoyl group, an optionally substituted C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), an optionally substituted C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, etc.), an optionally substituted C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), an optionally substituted C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.), an optionally substituted C_{1-6} alkylcarbonyloxy (e.g., acetoxy, propionyloxy, etc.), an optionally substituted C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.), an optionally substituted C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), an optionally substituted a mono-C_{1-6} alkylcarbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), an optionally substituted di-C_{1-6} alkylcarbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), an optionally substituted a mono- or di-C_{6-14} arylcarbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), an optionally substituted heterocyclic group, sulfo, sulfamoyl, sulfinamoyl, sulfenamoyl, or a group of 2 or more (e.g., 2 or 3) of these substituents combined, and the like (Substituent group A). The number of the substituents is not particularly limited but these rings may have 1 to 5, preferably 1 to 3 substituents in substitutable positions, and when there are two or more substituents, each substituent may be the same or different.

The "optionally esterified carboxyl used in the Substituent group A includes, for example, an optionally substituted C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), an optionally substituted C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), an optionally substituted C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The "C_{1-6} alkyl" in the "optionally substituted C_{1-6} alkyl" used in the Substituent group A includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

The "C_{2-6} alkenyl" in the "optionally substituted C_{2-6} alkenyl" used in the Substituent group A includes, for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl,

4-penten-1-yl, 5-hexen-1-yl, etc.

The "C_{2-6} alkynyl" in the "optionally substituted C_{2-6} alkynyl" used in the Substituent group A includes, for example, 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl, etc.

The "C_{3-8} cycloalkyl" in the "optionally substituted C_{3-8} cycloalkyl" used in the Substituent group A includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The C_{6-14} aryl in the optionally substituted C_{6-14} aryl used in the Substituent group A includes, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.

The "C_{7-16} aralkyl" in the "optionally substituted C_{7-16} aralkyl" used in the Substituent group A includes, for example, benzyl, phenethyl, diphenyllmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenyllethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl), etc.

The "C_{1-6} alkoxy" in the "optionally substituted C_{1-6} alkoxy" used in the Substituent group A includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The "C_{6-14} aryloxy" in the "optionally substituted C_{6-14} aryloxy" used in the Substituent group A includes, for example, phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.

The "C_{7-16} aralkyloxy" in the "optionally substituted C_{7-16} aralkyloxy" used in the Substituent group A includes, for example, benzyloxy, phenethyloxy, etc.

The "C_{1-6} alkylthio" in the "optionally substituted C_{1-6} alkylthio" used in the Substituent group A includes, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.

The "C_{6-14} arylthio" in the "optionally substituted C_{6-14} arylthio" used in the Substituent group A includes, for example, phenylthio, 1-naphthylthio, 2-naphthylthio, etc.

The "C_{7-16} aralkylthio" in the "optionally substituted C_{7-16} aralkylthio" used in the Substituent group A includes, for example, benzylthio, phenethylthio, etc.

The substituents used in the Substituent group A for these "C_{1-6} alkoxy-carbonyl," "C_{1-6} alkyl group," "C_{2-6} alkenyl," "C_{2-6} alkynyl," "C_{1-6} alkoxy," "C_{1-6} alkylthio," C_{1-6} alkyl-amino," C_{2-6} alkenyl-amino," "C_{2-6} alkynylamino," C_{1-6}

alkoxyamino," "C_{1-6} alkylcarbonyl," "C_{1-6} alkylsulfonyl," "C_{1-6} alkylsulfinyl," "C_{1-6} alkylcarbonylamino," "C_{1-6} alkoxy-carbonylamino," "C_{1-6} alkylsulfonylamino," "C_{1-6} alkylcarbonyloxy," "C_{1-6} alkoxy-carbonyloxy," "mono-C_{1-6} alkylcarbamoyloxy" and "di-C_{1-6} alkylcarbamoyloxy" include 1 to 5 substituents selected from, for example, a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom), carboxy, hydroxy, amino, a mono- or di-C_{1-6} alkylamino, a mono- or di-C_{6-14} arylamino, a C_{3-8} cycloalkyl, a C_{1-6} alkoxy, a C_{1-6} alkoxy-carbonyl, a C_{1-6} alkylthio, a C_{1-6} alkylsulfinyl, a C_{1-6} alkylsulfonyl, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), a di-C_{1-6} alkylcarbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), a mono- or di-C_{6-14} arylcarbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- to 7-membered heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.) and the like.

The substituents used in the Substituent group A for the "C_{6-14} aryloxy-carbonyl," "C_{7-16} aralkyloxy-carbonyl," "C_{3-8} cycloalkyl," "C_{6-14} aryl," "C_{7-16} aralkyl," "C_{6-14} aryloxy," "C_{7-16} aralkyloxy," "C_{6-14} arylthio," "C_{7-16} aralkylthio," C_{3-8} cycloalkyl-amino, C_{6-14} arylamino, "C_{3-8} cycloalkylcarbonyl," "C_{6-14} aryl-carbonyl," "C_{7-16} aralkylcarbonyl," "5- to 7-membered heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms," "C_{6-14} arylsulfonyl," "C_{6-14} arylsulfinyl," "C_{3-8} cycloalkylcarbonylamino," "C_{6-14} aryl-carbonylamino," "C_{6-14} arylsulfonylamino," "C_{6-14} aryl-carbonyloxy" and "mono- or di-C_{6-14} arylcarbamoyloxy" include 1 to 5 substituents selected from, for example, a halogen atom, hydroxy, carboxy, nitro, cyano, the optionally substituted C_{1-6} alkyl described above, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{1-6} alkoxy described above, the optionally substituted C_{1-6} alkylthio described above, the optionally substituted C_{1-6} alkylsulfinyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl, a di-C_{1-6} alkylcarbamoyl, a mono- or di-C_{6-14} arylcarbamoyl, a mono- or di-5- to 7-membered heterocyclic

carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, and the like.

The "optionally substituted heterocyclic group" used in the Substituent group A includes, for example, a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which may optionally be substituted with a halogen atom, hydroxy, carboxy, nitro, cyano, the optionally substituted C_{1-6} alkyl described above, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{6-14} aryl described above, the optionally substituted C_{1-6} alkoxy described above, the optionally substituted C_{1-6} alkylthio described above, the optionally substituted C_{6-14} arylthio described above, the optionally substituted C_{7-16} aralkylthio described above, the optionally substituted C_{1-6} alkylsulfinyl described above, the optionally substituted C_{6-14} arylsulfinyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, the optionally substituted C_{6-14} arylsulfonyl described above, the optionally esterified carboxyl described above, carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl, a di-lower alkylcarbamoyl, a mono- or di-C_{6-14} arylcarbamoyl, a mono- or di-5- or 7-membered heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, or the like; , preferably (i) a 5- to 14-membered (preferably, 5- to 10-membered) aromatic heterocyclic group, (ii) a 5- to 10-membered non-aromatic heterocyclic group or (iii) a monovalent group formed by one optional hydrogen atom from 7- to 10-membered bridged-hetero ring, and more preferably, a 5-memberedaromatic heterocyclic group. Specifically used are an aromatic heterocyclic group such as thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl, (e.g., 2-benzo[b]thienyl,

3-benzo[b]thienyl), benzo[b]furanyl (e.g., , 2-benzo[b]furanyl, 3-benzo[b]furanyl), etc., a non-aromatic heterocyclic group such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The "optionally substituted carbamoyl group" used in the Substituent group A includes a carbamoyl group, which may optionally be substituted with the optionally substituted C_{1-6} alkyl described above, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted C_{6-14} aryl, an optionally substituted heterocyclic group, etc., and specific examples are carbamoyl, thiocarbamoyl, a mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkylcarbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{1-6} alkyl(C_{1-6} alkoxy)carbamoyl (e.g., methyl(methoxy)carbamoyl, ethyl(methoxy)carbamoyl), a mono- or di-C_{6-14} arylcarbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), a mono- or di-5- to 7-memberedheterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), a 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, hexamethyleneiminocarbonyl), and the like.

The "optionally substituted amino" used in the Substituent group A includes an amino, which may optionally be substituted with 1 or 2 groups selected from the optionally substituted C_{1-6} alkyl, the optionally substituted C_{2-6} alkenyl described above, the optionally substituted C_{2-6} alkynyl described above, the optionally substituted C_{3-8} cycloalkyl described above, the optionally substituted C_{6-14} aryl described above, the optionally substituted C_{1-6} alkoxy described above described above, formyl, the optionally substituted C_{1-6} alkylcarbonyl described above, the optionally substituted C_{3-8} cycloalkylcarbonyl described above, the optionally substituted C_{6-14} aryl-carbonyl described above, the optionally substituted C_{1-6} alkoxy-carbonyl described above, the optionally substituted C_{1-6} alkylsulfonyl described above, an optionally substituted C_{6-14} arylsulfonyl) and the like.

More preferably, the substituents for the "C_{6-12} aromatic hydrocarbon group,"

"5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "C_{8-14} aromatic fused cyclic group," "5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7" and "non-aromatic heterocyclic group of carbon atoms not greater than 7" are a halogen atom, hydroxy, a C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkoxy, amino, nitro, cyano, etc.

Examples of R^4 used include:

(1) "a C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group" such as benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3,4-difluorobenzyl, 3,4-dichlorobenzyl, pentafluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 3-trifluoromethylbenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-cyanobenzyl, phenethyl, etc.;

(2) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 4-thiazolylmethyl, etc.;

(3) "a C_{1-4} alkyl group having an optionally substituted C_{8-14} aromatic fused cyclic group" such as 1-naphthylmethyl, 2-naphthylmethyl, inden-2-ylmethyl, etc.;

(4) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, etc.;

(5) "a C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" such as cyclohexylmethyl, cyclopentylmethyl, indan-2-ylmethyl, etc.;

(6) "a C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" such as 4-piperidinylmethyl, tetrahydrofurfuryl, tetrahydrofuran-2-yl, tetrahydropyran-3-yl, indolin-3-yl, etc., preferably, benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-aminobenzyl,

4-nitrobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-cyanobenzyl, 3-trifluoromethylbenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, pentafluorobenzyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclohexylmethyl, phenethyl, etc., and more preferably, に benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-cyanobenzyl, 3-trifluoromethylbenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, pentafluorobenzyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-indolemethyl, 3-benzo[b]thienylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclohexylmethyl, etc.

Q^1 represents a C_{1-4} alkyl group optionally substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7; and

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7; and the same substituents as in R^4 are used.

Examples of Q^1 include:

(1) "a C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group" such as benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 3,4-difluorobenzyl, 3,4-dichlorobenzyl, pentafluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-trifluoromethylbenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-cyanobenzyl, phenethyl, etc.;

(2) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 4-thiazolylmethy,

etc.;

(3)" a C_{1-4} alkyl group having optionally substituted C_{8-14} aromatic fused cyclic group," such as 1-naphthylmethyl, 2-naphthylmethyl, inden-2-ylmethyl;

(4) "a C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms" such as 3-indolemethyl, 1-formylindol-3-ylmethyl, 3-benzo[b]thienylmethyl, 2-quinolylmethyl, etc.;

(5) "a C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" such as cyclohexylmethyl, cyclopentylmethyl, indan-2-ylmethyl, etc.;

(6) "a C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" such as 4-piperidinylmethyl, tetrahydrofurfuryl, tetrahydrofuran-2-yl, tetrahydropyran-3-yl, indolin-3-yl, etc.; preferably, cyclohexylmethyl, benzyl, 4-fluorobenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, pentafluorobenzyl, 2-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 2-thienylmethyl, etc. and more preferably, benzyl, 4-fluorobenzyl, cyclohexylmethyl, etc.

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O.

Examples of the "C_{1-4} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

Preferably, Q^2 is CH_2, $CH(CH_3)$, $CH(CH_2OH)$, NH, or the like.

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group.

Examples of the "C_{1-6} alkyl group" used are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

Preferably, Y is a group represented by formula: -CONH-, -CSNH-, -NHCO-, $-CH_2NH-$, $-CH_2O-$, -COO- or -CSO- (more preferably, the group represented by formula: -CONH-, -CSNH-, -NHCO- or $-CH_2NH-$).

Z^9 represents hydrogen atom, O or S, preferably O or S;

wherein, when Z^9 represents hydrogen atom, a structure of the moiety represented by >C= Z^9 indicates a structure of $>CH_2$.

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula: J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(4) a group represented by formula: -J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(5) a group represented by formula: J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$- (wherein each symbol has the same significance as described above);

(6) a group represented by formula: J^1-J^2-$C(J^{12})(Q^{12})C(=Z^{10})$- (wherein each symbol has the same significance as described above); or,

(7) a group represented by formula:J^{1-} (wherein J^1 has the same significance as described above).

Specific examples of the "optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence represented by SEQ ID NO: 1" used include:

(1) Asn-

(2) Trp Asn-,

(3) Asn Trp Asn-,

(4) Tyr Asn Trp Asn-,

(5) Asn Tyr Asn Trp Asn-,

(6) Pro Asn Tyr Asn Trp Asn-,

(7) Leu Pro Asn Tyr Asn Trp Asn-,

(8) Asp Leu Pro Asn Tyr Asn Trp Asn-,

(9) Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(10) Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(11) Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(12) Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(13)Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(14) Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(15) Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(16) Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(17) Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(18) Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(19) Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(20) Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(21) Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(22) Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(23) Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(24) Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(25) Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(26) His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(27) Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(28) Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(29) Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(30) Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(31) Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(32) Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val

Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(33) Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(34) Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(35) Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(36) Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(37) Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(38) Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(39) Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(40) Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(41) Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(42) Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(43) Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(44) Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-;
(45) Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,
(46) Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu

Pro Asn Tyr Asn Trp Asn-,

(47) Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-,

(48) Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn-, etc.

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group.

The "cyclic group" used includes, for example, "an optionally substituted an aromatic hydrocarbon group," "an optionally substituted aromatic heterocyclic group," "an optionally substituted an aromatic fused cyclic group," "an optionally substituted an aromatic fused heterocyclic group," "an optionally substituted non-aromatic cyclic hydrocarbon group," "an optionally substituted non-aromatic heterocyclic group", etc., and as the "aromatic hydrocarbon group," "aromatic heterocyclic group," "aromatic fused cyclic group" and "aromatic fused heterocyclic group," the same groups given above are used.

The "non-aromatic cyclic hydrocarbon group" used includes, for example, a C_{3-8} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "non-aromatic heterocyclic group" used includes, for example, a 5- or 10-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 1 to 7 carbon atoms such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino, etc.

The substituent optionally present on the "cyclic group" includes the same substituents given for the Substituent group A described above.

The "C_{1-15} acyl group" used includes, for example, formyl, a C_{1-14} alkylcarbonyl (e.g., a C_{1-6} alkylcarbonyl such as acetyl, propionyl, pivaloyl, etc.) and the

like.

Examples of the "C_{1-15} alkyl group" used include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl, etc.

Examples of the "C_{6-14} aryl group" used include phenyl, 1-naphthyl, 2-naphthyl, biphenyl, etc.

(1) The C_{1-15} acyl group, which may optionally be substituted with a substituent containing a cyclic group, includes (i) formyl, (ii) a C_{1-14} alkylcarbonyl (e.g., a C_{1-6} alkylcarbonyl such as acetyl, propionyl, pivaloyl, etc.), (iii) a C_{3-8} cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 1-methylcyclohexylcarbonyl, etc.), (iv) a C_{3-8} cycloalkyl-C_{1-6} alkylcarbonyl (e.g., cyclopropylacetyl, cyclopentylacetyl, cyclohexylacetyl, etc.), (v) a C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), a C_{6-14} aralkylcarbonyl (e.g., phenylacetyl, 3-phenylpropionyl, etc.), (vi) a 5- to 7-membered monocyclic heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), (vii) a 5- to 7-membered monocyclic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylacetyl, 4-pyridylacetyl, 2-thienylacetyl, 2-furylacetyl, morpholinoacetyl, thiomorpholinoacetyl, piperidin-2-acetyl, pyrrolidine-2-ylacetyl, etc.), (viii) a 5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic carbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indolecarbonyl, 3-indolecarbonyl, 2-quinolylcarbonyl, 1-isoquinolylcarbonyl, 2-benzo[b]thienylcarbonyl, 2-benzo[b]furanylcarbonyl, etc.), (ix) a 5- to 14-membered (preferably 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indoleacetyl, 3-indoleacetyl, 2-quinolylacetyl, 1-isoquinolylacetyl, 2-benzo[b]thienylacetyl, 2-benzo[b]furanylacetyl, etc.), etc., preferably, acetyl, 2-indolecarbonyl, 3-indolecarbonyl, 3-indoleacetyl, 3-indolepropionyl, 2-indolinecarbonyl, 3-phenylpropionyl, diphenylacetyl, 2-pyridinecarbonyl, ,3-pyridinecarbonyl, ,4-pyridinecarbonyl, 1-pyridinioacetyl,

2-pyridineacetyl, ,3-pyridineacetyl, ,4-pyridineacetyl, 3-(1-pyridinio)propionyl, 3-(pyridin-2-yl)propionyl, 3-(pyridin-3-yl)propionyl, 3-(pyridin-4-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, 1-piperidineacetyl, 1-methyl-1-piperidinioacetyl, 4-piperidinecarbonyl, 2-pyrimidinecarbonyl, 4-pyrimidinecarbonyl, 5-pyrimidinecarbonyl, 2-pyrimidineacetyl, 4-pyrimidineacetyl, 5-pyrimidineacetyl, 3-(pyrimidine-2-yl)propionyl, 3-(pyrimidine-4-yl)propionyl, 3-(pyrimidine-5-yl)propionyl, butanoyl, hexanoyl, octanoyl, D-glucuronyl, amino-(4-hydroxyphenyl)acetyl), etc.

(2) The C_{1-15} alkyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a mono- or di-C_{1-15} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonanyl, decanyl), (ii) a mono- or di-C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclopentyl, etc.), (iii) a mono- or di-C_{3-8} cycloalkyl-C_{1-7} alkyl (e.g., cyclopropylmethyl, cyclopentylmethyl, cyclohexylethyl, etc.), (iv) a mono- or di-C_{7-15} aralkyl (e.g., benzyl, phenethyl, etc.), (v) a mono- or di-5- to 7-membered monocyclic heterocyclic-C_{1-6} alkyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylmethyl, 4-pyridylmethyl, 2-thienylmethyl, furfuryl, etc.), (vi) a mono- or di-5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkyl group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., 2-indolemethyl, 3-indolemethyl, 3-(indol-3-yl)propyl, 2-quinolylmethyl, 1-isoquinolylmethyl, 2-benzo[b]thienylmethyl, 2-benzo[b]furanylmethyl, etc.), etc., preferably, methyl, ethyl, benzyl, 3-(indol-3-yl)propyl, etc.

(3) The C_{6-14} aryl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, a C_{6-14} aryl group (e.g., phenyl, naphthyl, biphenyl), which may optionally be substituted with (i) a C_{6-14} carbocyclic group (e.g., cycloalkyl, phenyl, 1-naphthyl, 2-naphthyl, etc.), (ii) a 5- to 7-membered monocyclic heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridyl, 2-thienyl, etc.), (iii) a 5- to 14-membered containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic group (e.g., 2-indolyl, 3-indolyl, 2-quinolyl, 1-isoquinolyl,

2-benzo[b]thienyl, 2-benzo[b]furanyl, etc.), etc.

(4) The optionally substituted carbamoyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) carbamoyl, (ii) a mono- or di-C_{1-15} alkylcarbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, (iii) a mono- or di-C_{3-8} cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, etc.), (iv) a mono- or di-C_{3-8} cycloalkyl-C_{1-6} alkyl-carbamoyl (e.g., cyclopropylmethylcarbamoyl, cyclopentylmethylcarbamoyl, 2-cyclohexylethylcarbamoyl, etc.) (v) a mono- or di-C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, etc.), a mono- or di-C_{6-14} aralkyl-carbamoyl (e.g., benzylcarbamoyl, phenethylcarbamoyl, etc.), (vi) a mono- or di-5- to 7-membered monocyclic heterocyclic carbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridinecarbamoyl, 2-thiophenecarbamoyl, piperidin-3-ylcarbamoyl, etc.), (vii) a mono- or di-5- to 7-membered monocyclic heterocyclic-C_{1-6} alkylcarbamoyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms (e.g., 3-pyridylmethylcarbamoyl, 2-(pyridin-2-yl)ethylcarbamoyl, 2-(piperidin-1-yl)ethylcarbamoyl, etc.), (viii) a mono- or di-5- to 14-membered containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic carbamoyl (e.g., 4-indolecarbamoyl, 5-indolecarbamoyl, 3-quinolylcarbamoyl, 5-quinolylcarbamoyl, etc.), (ix) a mono- or di-5- to 14-membered (preferably, 5- to 10-membered) bicyclic or tricyclic aromatic heterocyclic-C_{1-6} alkylcarbonyl containing 1 to 4 hetero atoms of 1 or 2 species selected from nitrogen, sulfur and oxygen atoms in addition to 3 to 11 carbon atoms (e.g., benzimidazole-2-ylmethylcarbamoyl, 2-(indol-3-yl)ethylcarbamoyl, etc.), (x) a 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, hexamethyleneiminocarbonyl, etc.), (xi) a C_{1-15} acylcarbamoyl (the C_{1-15} acyl herein has the same significance as for the "C_{1-15} acyl group" in the "C_{1-15} acyl group used, which may optionally be substituted with a substituent containing a cyclic group"), (xii) a C_{1-15} alkylaminocarbamoyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group"), (xiii) a C_{6-14} arylaminocarbamoyl (the C_{6-14} aryl group herein has the same significance as for the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a

cyclic group"), etc., preferably, 2-(indol-3-yl)ethylcarbamoyl, etc.

(5) The carboxyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkyloxycarbonyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., tert-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), (ii) a C_{6-14} aryloxycarbonyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., phenoxycarbonyl), etc.

(6) The sulfino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkylsulfonyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., benzylsulfonyl), (ii) a C_{6-14} arylsulfonyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., tosyl), etc.

(7) The amidino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) amidino, (ii) a C_{1-15} alkylamidino (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., N-methylamidino), (iii) a C_{1-15} acylamidino (the C_{1-15} acyl herein has the same significance as for the "C_{1-15} acyl group" in the "C_{1-15} acyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., N-acetylamidino), etc.

(8) The glyoxyloyl group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkyloxalyl (the C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., ethyloxalyl), (ii) a C_{6-14} aryloxalyl (the C_{6-14} aryl herein has the same significance as for the "C_{6-14} aryl group" in the "C_{6-14} aryl group, which may optionally be substituted with a substituent containing a cyclic group," e.g., phenyloxalyl), etc.

(9) The amino group used, which may optionally be substituted with a substituent containing a cyclic group, includes, for example, (i) a C_{1-15} alkylamino (the

C_{1-15} alkyl herein has the same significance as for the "C_{1-15} alkyl group" in the "C_{1-15} alkyl group, which may optionally be substituted with a substituent containing a cyclic group."

Among those described above, J^1 is preferably hydrogen atom, formyl, acetyl, 3-indolecarbonyl, 3-(indol-3-yl)propionyl, 3-phenylpropionyl, diphenylacetyl, 3-(pyridin-3-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, 1-piperidineacetyl, 1-methyl-1-piperidinioacetyl, 4-piperidinecarbonyl, hexanoyl, amino-(4-hydroxyphenyl)acetyl, D-glucuronyl, 2-(indol-3-yl)ethylcarbamoyl, tert-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, amidino, 4-guanidomethylbenzoyl, benzoyl, 3-indoleacetyl, benzyloxycarbonyl, tosyl, phenyl, benzyl, phenethyl, 3-pyridinecarbonyl, 2-pyridinecarbonyl, 4-pyridinecarbonyl, propionyl, isobutyryl, phenylacetyl, 2-methylnicotinoyl, 5-methylnicotinoyl, 6-methylnicotinoyl, pyrazinecarbonyl, cyclopropanecarbonyl, trifluoroacetyl, (R)-3-hydroxy-2-methylpropionyl, 2-hydroxyisobutyryl, 3-furancarbonyl, pyrrole-2-carbonyl, 4-imidazolecarbonyl, 6-hydroxynicotinoyl, 6-chloronicotinoyl, 6-(trifluoromethyl)nicotinoyl, dimethylcarbamoyl, 1-azetidinecarbonyl, 2-azetidinecarbonyl, 4-aminobenzoyl, 4-aminomethylbenzoyl, pyrrole-3-carbonyl, pyrimidine-4-carbonyl, pyrimidine-2-carbonyl, pyridazine-4-carbonyl, 6-aminocaproyl, glycyl, glycylglycyl, glycylglycylglycyl, alanylalanylalanyl, alanylalanylalanylalanyl, acetylglycyl, acetylglycylglycyl, acetylglycylglycylglycyl, acetylalanylalanylalanyl, acetylalanylalanylalanylalanyl, D-arginylglycyl, D-arginylglycylglycyl, D-arginylglycylglycylglycyl, D-arginylalanylalanylalanyl, D-arginylalanylalanylalanylalanyl, acetyl-D-arginylglycyl, acetyl-D-arginylglycylglycyl, acetyl-D-arginylglycylglycylglycyl, acetyl-D-arginylalanylalanylalanyl, acetyl-D-arginylalanylalanylalanylalanyl, cyclopropanecarbonyl, cyclopentanecarbonyl, cyclobutanecarbonyl, cyclohexanecarbonyl, 1-naphthoyl, 2-naphthoyl, arginyl, arginylarginyl, 6-(arginylamino)caproyl, 6-(D-arginylamino)caproyl, 6-(D-arginyl-D-arginylamino)caproyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 3-(D-arginylamino)propionyl, 4-(D-arginylamino)butyryl, 4-(D-arginyl-D-arginylamino)butyryl, 4-(D-arginyl-D-arginyl-D-arginylamino)butyryl, 3-(4-hydroxyphenyl)propionyl, butyryl, methyl, adipoyl, pyroglutamyl, glycoloyl, etc., and more preferably used are hydrogen atom, formyl, acetyl, propionyl,

3-indolecarbonyl, 3-(indol-3-yl)propionyl, 3-phenylpropionyl, 3-(pyridin-3-yl)propionyl, 4-imidazoleacetyl, cyclohexanecarbonyl, hexanoyl, amino-(4-hydroxyphenyl)acetyl, 2-(indol-3-yl)ethylcarbamoyl, 9-fluorenylmethoxycarbonyl, amidino, 4-guanidomethylbenzoyl, benzoyl, 3-indoleacetyl, benzyl, phenethyl, 3-pyridinecarbonyl, 2-pyridinecarbonyl, 4-pyridinecarbonyl, isobutyryl, phenylacetyl, 6-methylnicotinoyl, pyrazinecarbonyl, cyclopropanecarbonyl, trifluoroacetyl, (R)-3-hydroxy-2-methylpropionyl, 2-hydroxyisobutyryl, 3-furancarbonyl, pyrrole-2-carbonyl, 4-imidazolecarbonyl, 6-hydroxynicotinoyl, 6-chloronicotinoyl, 6-(trifluoromethyl)nicotinoyl, dimethylcarbamoyl, 1-azetidinecarbonyl, 4-aminobenzoyl, 4-aminomethylbenzoyl, pyrrole-3-carbonyl, pyrimidine-4-carbonyl, pyrimidine-2-carbonyl, pyridazine-4-carbonyl, 6-aminocaproyl, cyclopropanecarbonyl, 2-naphthoyl, arginyl, 6-(arginylamino)caproyl, 6-(D-arginylamino)caproyl, 6-(D-arginyl-D-arginylamino)caproyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 3-(D-arginylamino)propionyl, 4-(D-arginylamino)butyryl, 4-(D-arginyl-D-arginylamino)butyryl, 4-(D-arginyl-D-arginyl-D-arginylamino)butyryl, 3-(4-hydroxyphenyl)propionyl, butyryl, adipoyl, pyroglutamyl, etc.

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S.

The "C_{1-6} alkyl group" used includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

Preferably, J^2 is NH.

J^3 through J^{12} each represents hydrogen atom or a C_{1-3} alkyl group.

The "C_{1-3} alkyl group" used includes methyl, ethyl, propyl, isopropyl, etc.

Preferably, J^3 is hydrogen atom.

Preferably, J^4 is hydrogen atom.

Preferably, J^5 is hydrogen atom.

Preferably, J^6 is hydrogen atom.

Preferably, J^7 is hydrogen atom.

Preferably, J^8 is hydrogen atom.

Preferably, J^9 is hydrogen atom.

Preferably, J^{10} is hydrogen atom.

Preferably, J^{11} is hydrogen atom.

Preferably, J^{12} is hydrogen atom.

Q^3 through Q^{12} each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7;

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

(7) an optionally substituted amino group;

(8) an optionally substituted guanidino group;

(9) an optionally substituted hydroxyl group;

(10) an optionally substituted carboxyl group;

(11) an optionally substituted carbamoyl group; and,

(12) an optionally substituted sulfhydryl group;

or hydrogen atom.

Preferably, Q^3 through Q^9 include a C_{1-4} alkyl group having a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group;

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(3) an optionally substituted C_{8-14} aromatic fused cyclic group;

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms;

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7;

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

(7) an optionally substituted amino group;

(8) an optionally substituted guanidino group;

(9) an optionally substituted hydroxyl group;

(10) an optionally substituted carboxyl group;

(11) an optionally substituted carbamoyl group; and,

(12) an optionally substituted sulfhydryl group;

or hydrogen atom.

The "optionally substituted C_{6-12} aromatic hydrocarbon group," "optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "optionally substituted C_{8-14} aromatic fused cyclic group," "optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms," "optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7" and "optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7" used are the same as those given above.

(1) As the C_{1-4} alkyl group having an optionally substituted C_{6-12} aromatic hydrocarbon group, there are used, for example, benzyl, 4-hydroxybenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, etc.

(2) As the C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, there are used, for example, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 4-imidazolemethyl, etc.

(3) As the C_{1-4} alkyl group having an optionally substituted C_{8-14} aromatic fused cyclic group, there are used, for example, 1-naphthylmethyl, 2-naphthylmethyl, etc.

(4) As the C_{1-4} alkyl group having an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, there are used, for example, 3-indolemethyl, 1-formylindol-3-ylmethyl, 2-quinolylmethyl, etc.

(5) As the C_{1-4} alkyl group having an optionally substituted non-aromatic cyclic

hydrocarbon group having carbon atoms not greater than 7, there are used, for example, cyclohexylmethyl, etc.

(6) As the C_{1-4} alkyl group having an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7, there are used, for example, piperidin-1-ylmethyl, etc.

(7) As the C_{1-4} alkyl group having an optionally substituted amino group, there are used, for example, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 4-acetamidobutyl, etc.

(8) As the C_{1-4} alkyl group having an optionally substituted guanidino group, there are used, for example, 3-guanidinopropyl, 3-(N-tosyl)guanidinopropyl, etc.

(9) As the C_{1-4} alkyl group having an optionally substituted hydroxyl group, there are used, for example, hydroxymethyl, 1-hydroxyethyl, benzyloxymethyl, etc.

(10) As the C_{1-4} alkyl group having an optionally substituted carboxyl group, there are used, for example, carboxylmethyl, 2-carboxylethyl, benzyloxycarbonylmethyl, etc.

(11) As the C_{1-4} alkyl group having an optionally substituted carbamoyl group, there are used, for example, carbamoylmethyl, 2-carbamoylethyl, xanthylcarbamoyl, etc.

(12) As the C_{1-4} alkyl group having an optionally substituted sulfhydryl group, there are used, for example, sulfhydrylmethyl, 2-(methylsulfhydryl)ethyl, etc.

(13) As the unsubstitued C_{1-4} alkyl group, there are used, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.

Preferably, Q^3 is hydrogen atom, 4-hydroxybenzyl, 3-pyridylmethyl, 4-pyridylmethyl, methyl, isobutyl, hydroxymethyl, carboxymethyl, 4-aminobutyl, etc., and more preferably, 4-hydroxybenzyl, 3-pyridylmethyl, 4-pyridylmethyl, etc.

Preferably, Q^4 includes carbamoylmethyl, 2-carbamoylethyl, 4-hydroxybenzyl, 4-imidazolemethyl, isobutyl, hydroxymethyl, 1-hydroxyethyl, carboxymethyl, 4-aminobutyl, etc., and more preferably, carbamoylmethyl, 2-carbamoylethyl, 4-hydroxybenzyl, etc.

Preferably, Q^5 includes benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 1-formylindol-3-ylmethyl, 2-quinolylmethyl, cyclohexylmethyl, hydroxymethyl, 1-hydroxyethyl, methyl, isopropyl, isobutyl, sec-butyl, carboxymethyl, 4-aminobutyl, etc., more preferably,

benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 4-aminobenzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-indolemethyl, 2-quinolylmethyl, cyclohexylmethyl, 1-hydroxyethyl, isopropyl, isobutyl, sec-butyl, etc.

Preferably, Q^6 is methyl, hydroxymethyl, 1-hydroxyethyl, carbamoylmethyl, 2-carbamoylethyl, etc., more preferably, carbamoylmethyl, etc.

Preferably, Q^7 is 4-hydroxybenzyl, carbamoylmethyl, 3-pyridylmethyl, methyl, isobutyl, benzyl, 4-aminobutyl, 3-indolemethyl, etc., more preferably, 4-hydroxybenzyl, etc.

Preferably, Q^8 is benzyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-naphthylmethyl, 3-indolemethyl, hydroxymethyl, cyclohexylmethyl, sec-butyl, 1-hydroxyethyl, methyl, methyl, isobutyl, 4-aminobutyl, 3-carboxypropyl, etc., more preferably, 4-pyridylmethyl, 3-indolemethyl, sec-butyl, etc.

Preferably, Q^9 is hydrogen atom, methyl, ethyl, hydroxymethyl, 1-hydroxyethyl, carbamoylmethyl, 2-carbamoylethyl, ureidomethyl, acetamidomethyl, formamidemethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, etc., more preferably, carbamoylmethyl, ureidomethyl, etc.

Preferably, Q^{10} is 4-hydroxybenzyl, 3-indolemethyl, methyl, 1-hydroxyethyl, 3-guanidinopropyl, etc., more preferably, 3-indolemethyl, etc.

Preferably, Q^{11} is carbamoylmethyl, etc.

Preferably, Q^{12} is methyl, carbamoylmethyl, etc., more preferably, carbamoylmethyl, etc.

Y^1 through Y^3 each represents a group represented by formula: $-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group).

As the C_{1-3} alkyl group represented by J^{13} and J^{14}, there is used methyl, ethyl, propyl or isopropyl.

J^{13} is hydrogen atom.

J^{14} is hydrogen atom.

Y^1 is preferably a group represented by formula: $-CONH-$ or $-CH_2NH-$, etc.

Y^2 is preferably a group represented by formula: $-CONH-$ or $-CH_2NH-$, etc.

Y^3 is preferably a group represented by formula: $-CONH-$, etc..

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5, J^6 and Q^6, J^7 and Q^7, J^8 and Q^8, J^9 and Q^9, J^{10} and Q^{10}, J^{11} and Q^{11}, and J^{12} and Q^{12} may be combined together to form a ring. In this

case, for example, cyclopentane, cyclohexane, piperidine, etc. are formed by $C(J^3)(Q^3)$, $C(J^4)(Q^4)$, $C(J^5)(Q^5)$, $C(J^6)(Q^6)$, $C(J^7)(Q^7)$, $C(J^8)(Q^8)$, $C(J^9)(Q^9)$, $C(J^{10})(Q^{10})$, $C(J^{11})(Q^{11})$ or $C(J^{12})(Q^{12})$.

Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, J^2 and Q^7, Y^2 and Q^8, Y^3 and Q^9, J^2 and Q^{10}, Y^3 and Q^{11}, and J^2 and Q^{12} (preferably, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, J^2 and Q^7, Y^2 and Q^8, Y^3 and Q^9, J^2 and Q^{10}, Y^3 and Q^{11}, and J^2 and Q^{12}) may be combined together to form a ring. Alternatively, the ring formed may be optionally substituted, or annealed.

In the case where Z^1 and R^1, J^2 and Q^3, J^2 and Q^7, J^2 and Q^{10}, or J^2 and Q^{12} may be combined together to form a ring, for example, azetidine, pyrrolidine, piperidine or thiazolidine is formed by Z^1-N-CH-R^1, J^2-$C(J^3)(Q^3)$, J^2-$C(J^7)(Q^7)$, J^2-$C(J^{10})(Q^{10})$ or J^2-$C(J^{12})(Q^{12})$. Alternatively, the ring formed may be optionally substituted, or annealed. Z^1-N-CH-R^1 is preferably azetidine, pyrrolidine, 4-hydroxypyrrolidine, piperidine, etc.

In the case where Y^1 and Q^4, Y^2 and Q^5, Y^3 and Q^6, Y^2 and Q^8, Y^3 and Q^9, or Y^3 and Q^{11} may be combined together to form a ring, for example, pyrrolidine-2-carbonyl, piperidin-2-carbonyl or thiazolidine-4-carbonyl is formed by $Y^1C(J^4)(Q^4)$, $Y^2C(J^5)(Q^5)$, $Y^3C(J^6)(Q^6)$, $Y^2C(J^8)(Q^8)$, $Y^3C(J^9)(Q^9)$, or $Y^3C(J^{11})(Q^{11})$. Alternatively, the ring formed may be optionally substituted, or annealed.

Preferred examples of the group represented by formula: J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$- include:

Tyr Asn Trp Asn-,
Tyr Asn Trp D-Asn-,
Tyr Asn D-Trp Asn-,
Tyr D-Asn Trp Asn-,
D-Tyr Asn Trp Asn-,
Tyr Lys Trp Asn-,
Tyr Asp Trp Asn-,
Tyr Tyr Trp Asn-,
Tyr Leu Trp Asn-,
Tyr Asn Ala Asn-,
Tyr Asn Leu Asn-,
Tyr Asn Ser Asn-,
Tyr Asn Asp Asn-,

Tyr Asn Lys Asn-,

Ala Asn Trp Asn-,

Leu Asn Trp Asn-,

Ser Asn Trp Asn-,

Asp Asn Trp Asn-,

Lys Asn Trp Asn-,

Tyr Asn Trp(For)Asn-,

D-Tyr Asn D-Trp Asn-,

D-Tyr Asn Ala Asn-,

D-Tyr Asn Ser Asn-,

D-Tyr Asn Cha Asn-,

D-Tyr Asn Thr Asn-,

D-Tyr Asn Ile Asn-,

D-Tyr Gln Trp Asn-,

D-Tyr Thr Trp Asn-,

D-Tyr Asn Val Asn-,

D-Tyr D-Asn Trp Asn-,

D-Tyr D-Asn D-Trp Asn-,

D-Tyr Asn Phe Asn-,

D-Tyr Asn Nal(1) Asn-,

D-Tyr Asn Nal(2) Asn-,

D-Tyr Asn Phe(2Cl) Asn-,

D-Tyr Asn Phe(3Cl) Asn-,

D-Tyr Asn Phe(4Cl) Asn-,

D-Tyr Asn Phe($4NH_2$) Asn-,

D-Tyr Asn Pya(3) Asn-,

D-Tyr D-Asn Phe Asn-,

D-Tyr D-Asn Cha Asn-,

D-Tyr D-Asn Thr Asn-,

D-Tyr Asn Pya(2) Asn-,

D-Tyr Asn Pya(4) Asn-,

D-Tyr D-Ser Trp Asn-,

D-Tyr D-His Trp Asn-,

D-Pya(3) D-Asn Cha Asn-,

D-Pya(3) D-Tyr Cha Asn-,

TyrΨ(CH_2NH)Asn Trp Asn-,

D-Tyr AsnΨ(CH_2NH)Trp Asn-,

TyrΨ(CH_2NH)Asn D-Trp Asn-,

D-Tyr Asn Ala(2-Qui) Asn-,

D-Tyr Asn D-Pya(4) Asn-,

D-Tyr D-Asn Pya(4) Asn-,

Tyr D-Asn Cha Asn-,

Dap D-Tyr Asn Trp Asn-

Arg D-Tyr D-Pya(4) Asn-

Arg Arg D-Tyr D-Pya(4) Asn-

Arg Acp D-Tyr D-Pya(4) Asn-

D-Arg Acp D-Tyr D-Trp Asn-

D-Arg D-Arg Acp D-Tyr D-Trp Asn-

Ac D-Arg Acp D-Tyr D-Trp Asn-

D-Dap Acp D-Tyr D-Trp Asn-

D-Nle Acp D-Tyr D-Trp Asn-

D-Arg β-Ala D-Tyr D-Trp Asn-

D-Arg γ-Abu D-Tyr D-Trp Asn-

D-Arg D-Arg γ-Abu D-Tyr D-Trp Asn-

D-Arg D-Arg D-Arg γ-Abu D-Tyr D-Trp Asn-

Gly D-Tyr D-Trp Asn-

Ac Gly D-Tyr D-Trp Asn-

D-Tyr D-Tyr D-Trp Asn-

Ac D-Tyr D-Tyr D-Trp Asn-

pGlu D-Tyr D-Trp Asn-

Tyr D-Tyr D-Trp Asn-

Ac Tyr D-Tyr D-Trp Asn-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})- include:

Fmoc Asn Trp Asn-,

D-Asn Trp Asn-,

D-Tyr Trp Asn-,

D-Tyr D-Trp Asn-,

D-Tyr Ser Asn-,
D-Tyr Thr Asn-,
D-Tyr Ile Asn-,
D-Tyr Phe Asn-,
D-Tyr Nal(2) Asn-,
D-Pya(3) Phe Asn-,
D-Pya(3) Trp Asn-,
D-Tyr D-Pya(4) Asn-,
D-Asn Cha Asn-
D-Tyr D-Pya(4) Ala-
D-Tyr D-Pya(4) Thr-
D-Tyr Pya(4) Ala-
D-Tyr D-Trp Ala-
D-Tyr D-Trp Abu-
D-Tyr D-Phe Ala-6-Aminocaproyl-
D-Tyr D-Pya(4) Asn-
Ac D-Tyr D-Pya(4) Asn-
Benzoyl D-Tyr D-Trp Asn-
Cyclopropanecarbonyl D-Tyr D-Trp Asn-
Butyryl D-Tyr D-Trp Asn-
Me D-Tyr D-Trp Asn-
Ac D-Tyr D-Trp Gln-
Ac D-Tyr D-Trp Ser-
Ac D-Tyr D-Trp Thr-
Ac D-Tyr D-Trp Alb-
Ac D-Tyr D-Trp Dap(Ac)-
Ac D-Tyr D-Trp Dap(For)-
Ac D-Tyr Trp Asn-
Ac D-NMeTyr D-Trp Asn-
For D-Tyr D-Trp Asn-
Propionyl D-Tyr D-Trp Asn-
Amidino D-Tyr D-Trp Asn-
Ac D-Ala D-Trp Asn-
Ac D-Leu D-Trp Asn-

Ac D-Phe D-Trp Asn-
Ac D-Nal(1) D-Trp Asn-
Ac D-Nal(2) D-Trp Asn-
Ac D-Lys D-Trp Asn-
Ac D-Glu D-Trp Asn-
Ac D-Tyr D-Ala Asn-
Ac D-Tyr D-Leu Asn-
Ac D-Tyr D-Phe Asn-
Ac D-Tyr D-Thr Asn-
Ac D-Tyr D-Lys Asn-
Ac D-Tyr D-Glu Asn-
Ac D-Tyr D-Trp Asp-
Ac D-Tyr D-Trp D-Asn-
Ac D-Tyr D-Trp NMeAsn-
Ac D-Tyr Pro Asn-
Ac D-Tyr D-Pya(2) Asn-
Ac D-Tyr D-Pya(3) Asn-
Ac D-Tyr D-Pro Asn-
Ac D-Tyr Tic Asn-
Ac Tyr Trp Asn-
Ac D-Tyr NMeTrp Asn-
Glycoloyl D-Tyr D-Trp Asn-
Ac D-Tyr D-Trp Gly-
Ac D-Tyr D-Trp Dap-
Ac D-Tyr D-Trp Asp(NHMe)-
Ac D-Tyr D-Trp Asp(NMe2)-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$- include:

Fmoc Trp Asn-,
Boc Tyr Asn-,
Tyr Asn-,
D-Trp Asn-,
Ac Trp Asn-,
Amidino Trp Asn-,

Ac Ala Asn-,

Ac Arg Asn-,

Ac Thr Asn-

D-Tyr D-Pya(4)-

3-(4-Hydroxyphenyl)propionyl D-Trp Asn-

D-Trp Asn-

Ac D-Trp Asn-

Hexanoyl D-Trp Asn-

Cyclohexanecarbonyl D-Trp Asn-

Benzoyl D-Trp Asn-

3-Pyridinepropionyl D-Trp Asn-

Adipoyl D-Trp Asn-

6-Aminocaproyl D-Trp Asn-

Amidino D-Trp Asn-

Glycoloyl D-Trp Asn-, and the like.

Preferred examples of the group represented by formula: J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})- include:

Fmoc Asn-,

3-(Indol-3-yl)propionyl Asn-,

3-Indolecarbonyl Asn-,

3-Indoleacetyl Asn-,

4-(Indol-3-yl)butyryl Asn-,

Diphenylacetyl Asn-,

Hexanoyl Asn-,

Cyclohexanecabonyl Asn-,

2-(Indol-3-yl)ethylcabamoyl Asn-,

3-(3-Pyridyl)propionyl Asn-,

4-Imidzoleacetyl Asn-,

Piperidinecarbonyl Asn-,

1-Piperidineacetyl Asn-,

1-Methyl-1-piperidinioacetyl Asn-,

1-Pyridinioacetyl Asn-,

D-Glucuronyl Asn-,

3-Phenylpropionyl Asn-,

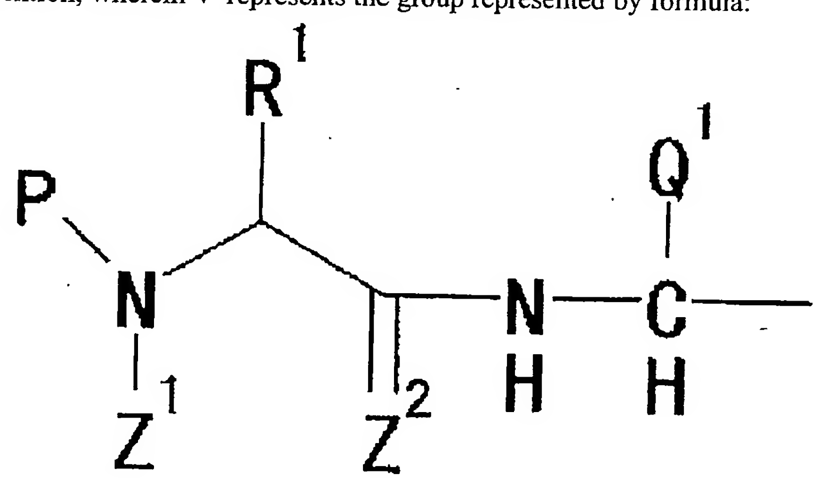
3-Phenylpropionyl Ala-,
Benzoyl Asn-,
Ac Asn-,
Cyclopropanecarbonyl Asn-,
2-Naphthoyl Asn-, and the like.

Preferred examples of the group represented by formula: J^{1-} include:

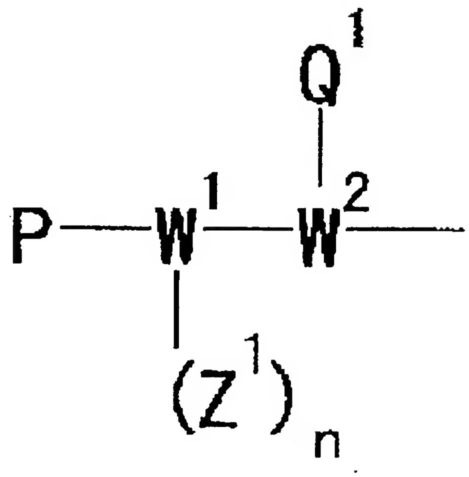
hydrogen atom,
GuAmb-,
3-(3-Indolyl)propionyl-,
3-(3-Pyridyl)propionyl-,
Benzoyl-,
Indole-3-carbonyl-,
Indole-3-acetyl-,
Ac-,
Hexanoyl-,
Z-,
Tos-,
3-Phenylpropionyl-,
2-(Indol-3-yl)ethylcarbamoyl-,
Benzyl-,
Phenethyl-,
2-Pyridinecarbonyl-,
4-Pyridinecarbonyl-,
Propionyl-,
Isobutyryl-,
Cyclohexanecarbonyl-,
Phenylacetyl-,
2-Methylnicotinoyl-,
5-Methylnicotinoyl-,
6-Methylnicotinoyl-,
Pyrazinecarbonyl-,
Cyclopropanecarbonyl-,
Trifluoroacetyl-,
(R)-3-hydroxy-2-methylpropionyl-,

2-Hydroxyisobutyryl-,
3-Furancarbonyl-,
Pyrrole-2-carbonyl-,
4-Imidazolecarbonyl-,
6-Hydroxynicotinoyl-,
6-Chloronicotinoyl-,
6-(Trifluoromethyl)nicotinoyl-,
Dimethylcarbamoyl-,
1-Azetidinecarbonyl-,
2-Azetidinecarbonyl-,
4-Aminobenzoyl-,
4-Aminomethylbenzoyl-,
Pyrrole-3-carbonyl-,
Pyrimidine-4-carbonyl-,
Pyrimidine-2-carbonyl-,
Pyridazine-4-carbonyl-, and the like.

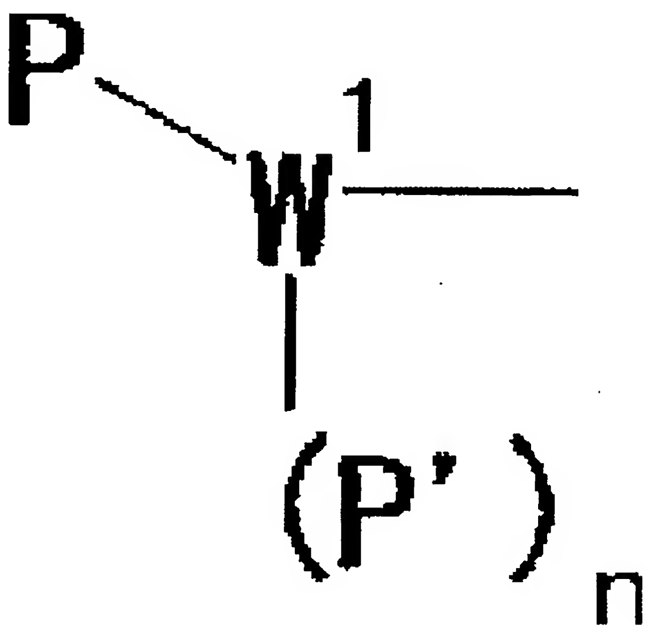
The metastin derivatives (I) in the metastin derivatives (III) of the present invention, wherein V' represents the group represented by formula:



(wherein each symbol has the same significance as defined above) are a class of compound disclosed in the specification filed as PCT/JP03/16978, whereas the metastin derivatives (II), wherein V' represents the group represented by formula:



(wherein each symbol has the same significance as defined above), or the group represented by formula:



(wherein each symbol has the same significance as defined above) are novel compounds.

In the metastin derivatives (III), all compounds that the groups shown by the respective symbols are optionally combined are preferably used. Among them, the compounds shown by Compound Numbers below (TABLES 1 through 11) are

preferred.

MS10 :Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

1 2 3 4 5 6 7 8 9 10

Compound No. 17: [Pya(4)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(4)-NH_2

Compound No. 18: [Tyr(Me)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr(Me)-NH_2

Compound No. 19: [Phe(2F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(2F)-NH_2

Compound No. 23: [Tyr5]MS10

Tyr-Asn-Trp-Asn-Tyr-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 24: [Leu5]MS10

Tyr-Asn-Trp-Asn-Leu-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 30: Acetyl-MS10

Acetyl-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 31: Fmoc-MS10

Fmoc-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 38: [D-Ser5]MS10

Tyr-Asn-Trp-Asn-D-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 39: [D-Asn4]MS10

Tyr-Asn-Trp-D-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 40: [D-Trp3]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 41: [D-Asn2]MS10

Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 42: [D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 44: [Lys9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys-Phe-NH2

Compound No. 45: [Ala8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Ala-Arg-Phe-NH_2

Compound No. 50: [Ala7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg-Phe-NH_2

Compound No. 51: [NMePhe10]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-NMePhe-NH_2
Compound No. 53: des(1-3)-Fmoc-MS10
Fmoc-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 54: des(1-2)-Fmoc-MS10
Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 55: des(1)-Fmoc-MS10
Fmoc-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 56: [Lys2]MS10
Tyr-Lys-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 57: [Asp2]MS10
Tyr-Asp-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 58: [Tyr2]MS10
Tyr-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 59: [Leu2]MS10
Tyr-Leu-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 60: [Pya(3)10]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Pya(3)-NH_2
Compound No. 61: [Phe(4F)10]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4F)-NH_2
Compound No. 67: [Ala3]MS10
Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 68: [Leu3]MS10
Tyr-Asn-Leu-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 69: [Ser3]MS10
Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 70: [Asp3]MS10
Tyr-Asn-Asp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 71: [Lys3]MS10
Tyr-Asn-Lys-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 72: [Ala1]MS10
Ala-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 73: [Leu1]MS10
Leu-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 74: [Ser1]MS10

Ser-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 75: [Asp1]MS10

Asp-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 76: [Lys1]MS10

Lys-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 77: [Phe(4CN)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compound No. 78: [Trp(For)3, Phe(4CN)10]MS10

Tyr-Asn-Trp(For)-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4CN)-NH_2

Compound No. 79: [Hph10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Hph-NH_2

Compound No. 81: [NMeArg9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-NMeArg-Phe-NH_2

Compound No. 82: [Arg(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 83: [Arg(asy Me_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(asyMe_2)-Phe-NH_2

Compound No. 87: des(4-5)-Boc-MS10

Boc-Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 88: des(4-5)-MS10

Tyr-Asn-Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 90: [Lys9,9Ψ10,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-LysΨ(CH_2NH)Phe-NH_2

Compound No. 91: [8Ψ9,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-LeuΨ(CH_2NH)Arg-Phe-NH_2

Compound No. 97: [Har9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har-Phe-NH_2

Compound No. 98: [Lys(Me_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Lys(Me_2)-Phe-NH_2

Compound No. 101: [Ser7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Ser-Leu-Arg-Phe-NH_2

Compound No. 105: [Nle8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Nle-Arg-Phe-NH_2

Compound No. 107: [Val8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg-Phe-NH_2

Compound No. 109: [Tyr10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr-NH_2

Compound No. 110: [Nal(2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(2)-NH_2

Compound No. 111: [Phe(F5)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(F5)-NH_2

Compound No. 112: [Cha10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Cha-NH_2

Compound No. 114: des(1-3)-3-(3-Indolyl)propionyl-MS10

3-(3-Indolyl)propionyl-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 121: des(1-4)-[Trp5]MS10

Trp-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 123: [NMeLeu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-NMeLeu-Arg-Phe-NH_2

Compound No. 126: [NMeSer5]MS10

Tyr-Asn-Trp-Asn-NMeSer-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 127: [D-Asn4,NMePhe6]MS10

Tyr-Asn-Trp-D-Asn-Ser-NMePhe-Gly-Leu-Arg-Phe-NH_2

Compound No. 128: [10Ψ,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-PheΨ(CSNH)NH_2

Compound No. 129: [Arg(symMe_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(symMe_2)-Phe-NH_2

Compound No. 130: [Phe(4Cl)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4Cl)-NH_2

Compound No. 131: [Phe(4NH_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NH_2)-NH_2

Compound No. 132: [Phe(4NO_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(4NO_2)-NH_2

Compound No. 133: [Nal(1)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Nal(1)-NH_2

Compound No. 134: [Trp10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp-NH_2

Compound No. 137: [Nle9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nle-Phe-NH_2

Compound No. 138: [Cit9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Cit-Phe-NH_2

Compound No. 140: [Arg(Me)9,NMePhe10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-NMePhe-NH_2

Compound No. 141: [D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 142: [D-Tyr1,D-Trp3,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 143: [D-Trp3,Arg(Me)9]MS10

Tyr-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 144: des(1-3)-Fmoc-[Arg(Me)9]MS10

Fmoc-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 145: des(1-2)-Fmoc-[Arg(Me)9]MS10

Fmoc-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 146: [10Ψ,CSNH,D-Tyr1]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-PheΨ(CSNH)NH_2

Compound No. 150: [Tyr6]MS10

Tyr-Asn-Trp-Asn-Ser-Tyr-Gly-Leu-Arg-Phe-NH_2

Compound No. 151: [Nal(1)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(1)-Gly-Leu-Arg-Phe-NH_2

Compound No. 152: [Nal(2)6]MS10

Tyr-Asn-Trp-Asn-Ser-Nal(2)-Gly-Leu-Arg-Phe-NH_2

Compound No. 153: [Phe(F5)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(F_5)-Gly-Leu-Arg-Phe-NH_2

Compound No. 154: [Phe(4F)6]MS10

Tyr-Asn-Trp-Asn-Ser-Phe(4F)-Gly-Leu-Arg-Phe-NH_2

Compound No. 156: [Cha6]MS10

Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg-Phe-NH_2

Compound No. 163: [6Ψ7,CH_2NH]MS10

Tyr-Asn-Trp-Asn-Ser-PheΨ(CH_2NH)Gly-Leu-Arg-Phe-NH_2

Compound No. 165: [Dap(Gly)9]-MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(Gly)-Phe-NH_2

Compound No. 166: [6Ψ7,CSNH]MS10

Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg-Phe-NH_2

Compound No. 169: [D-Tyr1,Ala3,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 170: [D-Tyr1,Ser3,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 171: [D-Tyr1,Cha3,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 172: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 173: [D-Tyr1,Ala7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compound No. 174: [D-Tyr1,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 176: [AzaGly7]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compound No. 181: [D-Tyr1,Cha3,6,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 182: [D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10

D-Tyr-Asn-Cha-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 183: [Phe(4NH_2)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4NH_2)-Phe-NH_2

Compound No. 184: [Phe(4-Guanidino)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Phe(4-Guanidino)-Phe-NH_2

Compound No. 185: [Dap(GnGly)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dap(GnGly)-Phe-NH_2

Compound No. 186: [Trp(For)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Trp(For)-NH_2

Compound No. 187: [Abu8]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Abu-Arg-Phe-NH_2

Compound No. 189: [Ala(3-Bzt)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(3-Bzt)-NH_2

Compound No. 190: [D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 191: [D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 192: [D-Tyr1,Arg(Et)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2

Compound No. 193: [D-Tyr1,Arg(n-Pr)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(n-Pr)-Phe-NH_2

Compound No. 194: [D-Tyr1,Arg(Ac)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Ac)-Phe-NH_2

Compound No. 197: [Phe(3F)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3F)-NH_2

Compound No. 198: [Phe(3,4F_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4F_2)-NH_2

Compound No. 199: [Phe(3,4Cl_2)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3,4Cl_2)-NH_2

Compound No. 200: [Phe(3CF_3)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe(3CF_3)-NH_2

Compound No. 201: [Ala(2-Qui)10]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Ala(2-Qui)-NH_2

Compound No. 203: [D-Tyr1,Cha6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 204: [D-Tyr1, Ala7, Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-Ala-Leu-Arg(Me)-Phe-NH_2

Compound No. 205: [D-Tyr1,Thr3,Arg(Me)9]MS10

D-Tyr-Asn-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 206: [D-Tyr1,Ile3,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 207: [D-Tyr1,Ser4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ser-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 208: [D-Tyr1,Thr4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Thr-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 209: [D-Tyr1,Gln4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Gln-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 210: [D-Tyr1,Ala4,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Ala-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 211: [D-Tyr1,Thr5,Arg(Me)9]MS10
D-Tyr-Asn-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 212: [D-Tyr1,Ala5,Arg(Me)9]MS10
D-Tyr-Asn-Trp-Asn-Ala-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 213: [D-Tyr1,Val8,Arg(Me)9]MS10
D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Val-Arg(Me)-Phe-NH_2
Compound No. 214: [D-Tyr1,Gln2,Arg(Me)9]MS10
D-Tyr-Gln-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 215: [D-Tyr1,Thr2,Arg(Me)9]MS10
D-Tyr-Thr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 216: des(1)-[D-Asn2,Arg(Me)9]MS10
D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 217: des(1)-[D-Tyr2,Arg(Me)9]MS10
D-Tyr-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 218: [N((CH_2)$_3$Gn)]Gly9]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-N((CH_2)$_3$Gn)Gly-Phe-NH_2
Compound No. 220: [Arg(Et)9]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Et)-Phe-NH_2
Compound No. 221: [D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 222: des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10
D-Tyr-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 223: des(1-2)-[D-Trp3,Arg(Me)9]MS10
D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 224: des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10
D-Tyr-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 225: des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10
D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 226: des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10
D-Tyr-Ser-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 227: des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10
D-Tyr-Thr-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 228: des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10
D-Tyr-Ile-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 229: [D-Tyr1,Val3,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 230: [D-Tyr1,D-Asn2,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 231: [D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 232: [D-Tyr1,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 233: [D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 234: [D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Val-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 235: [D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 236: [D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 237: [D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 238: [D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 239: des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ser-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 240: des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Ile-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 241: des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 242: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 244: [D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 245: [D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(1)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 246: [D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 247: [D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Phe(2Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 248: [D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Phe(3Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 249: [D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Phe(4Cl)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 250: [D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Phe(4NH_2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 251: [D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Pya(3)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 252: [D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-D-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 253: [D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Asn-Pro-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 254: des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 255: des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Nal(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 256: des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10
D-Pya(3)-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 257: [D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10
D-Tyr-D-Asn-Phe-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 258: [D-Pya(3)1,AzaGly7,Arg(Me)9]MS10
D-Pya(3)-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 259: [D-Ala1,AzaGly7,Arg(Me)9]MS10
D-Ala-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 260: des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10
3-(3-Indolyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 261: [7Ψ8,CH_2NH]MS10
Tyr-Asn-Trp-Asn-Ser-Phe-GlyΨ(CH_2NH)Leu-Arg-Phe-NH_2
Compound No. 265: des(1-3)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10
Indole-3-carbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 266: des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10
Indol-3-acetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 267: des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7,Arg(Me)9]MS10

4-(3-Indolyl)butyryl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 268: des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)9]MS10

Diphenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 269: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10

3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 270: [D-Tyr1,Phe3,Ser-Phe5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Phe-Asn-Ser-Phe-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 271: des(1-2)-[AzaGly7,Arg(Me)9]MS10

Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 272: des(1-2)-Acetyl-[AzaGly7,Arg(Me)9]MS10

Acetyl-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 273: des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10

Amidino-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 274: des(1-2)-Acetyl-[Ala3,AzaGly7,Arg(Me)9]MS10

Acetyl-Ala-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 275: des(1-2)-Acetyl-[Arg3,AzaGly7,Arg(Me)9]MS10

Acetyl-Arg-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 276: des(1-2)-Acetyl-[Thr3,AzaGly7,Arg(Me)9]MS10

Acetyl-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 277: des(1-3)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10

n-Hexanoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 278: des(1-3)-Cyclohexanecarbonyl-[AzaGly7, Arg(Me)9]MS10

Cyclohexanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 279: des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10

2-(indol-3-yl)ethylcarbamoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 281: [D-Tyr1,Pya(2)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(2)-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 282: [D-Tyr1,Pya(4)6,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Pya(4)-Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 283: [D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 284: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 285: [D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(2)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 286: [D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 287: [D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Ser-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 288: [D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-His-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 289: des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 290: [D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 291: [D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(3)-D-Tyr-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 293: [4Ψ5,CH_2NH]MS10

Tyr-Asn-Trp-AsnΨ(CH_2NH)Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 294: [1Ψ2,CH_2NH]MS10

TyrΨ(CH_2NH)Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 295: [2Ψ3,CH_2NH]MS10

Tyr-AsnΨ(CH_2NH)Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Compound No. 296: [6Ψ7,CSNH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 297: [D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 298: [D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 299: [1Ψ2,CH_2NH,AzaGly7,Arg(Me)9]-MS10

TyrΨ(CH_2NH)Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 300: [1Ψ2,CH_2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10

TyrΨ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 301: [D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-Ala(2-Qui)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 302: [D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Asn-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 303: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 304: [D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 305: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 306: [D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Pya(4)-D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 307: [7Ψ8,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-GlyΨ(CH_2NH)Leu-Arg(Me)-Phe-NH_2

Compound No. 308: [6Ψ7,CH_2NH,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 310: [Nar9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar-Phe-NH_2

Compound No. 311: [Nar(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Nar(Me)-Phe-NH_2

Compound No. 312: [Har(Me)9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Har(Me)-Phe-NH_2

Compound No. 313: [Dab9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Dab-Phe-NH_2

Compound No. 314: [Orn9]MS10

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Orn-Phe-NH_2

Compound No. 315: des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10

D-Asn-Cha-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 316: [D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Thr-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 317: [D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 318: [D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 319: [6Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10

D-Tyr-Asn-Trp-Asn-Ser-PheΨ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2

Compound No. 322: des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10

3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 323: des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10
4-Imidazoleacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 324: des(1-3)-4-Piperidinecarbonyl-[AzaGly7,Arg(Me)9]MS10
Piperidinecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 325: des(1-3)-1-Piperidineacetyl-[AzaGly7,Arg(Me)9]MS10
1-Piperidineacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 326: des(1-3)-1-Methylpiperidinio-1-acetyl-[AzaGly7,Arg(Me)9]MS10
1-Methylpiperidino-1-acetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 327: des(1-3)-1-Pyridinioacetyl-[AzaGly7,Arg(Me)9]MS10
1-Pyridinoacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 328: des(1-3)-D-Glucuronyl-[AzaGly7,Arg(Me)9]MS10
D-Glucuronyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 375:2-Aminoethyl-Gly-[D-Tyr1,Arg(Me)9]MS10
2-Aminoethyl-Gly-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 385: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 386: des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
3-(3-Pyridyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 387:Dap-[D-Tyr1,Arg(Me)9]MS10
Dap-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 397:Methylthiocarbamoyl-Sar-[D-Tyr1,Arg(Me)9]MS10
Methylthiocarbamoyl-Sar-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 400:
(S)-1-(Quinolin-8-yl-carbamoyl)-4-thiapentylcarbamoyl-[D-Tyr1,Arg(Me)9]MS10
(S)-1-(Quinolin-8-yl-carbamoyl)-4-thiapentylcarbamoyl-D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 481: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2
Compound No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2
Compound No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2
Compound No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compound No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2
Compound No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10
D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 494: des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2
Compound No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 499: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 500:
des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 503: des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10
Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 505:

des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 506: des(1-3)-3-Phenylpropionyl-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 507: des(1-3)-3-Phenylpropionyl-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 508: des(1-3)-3-Phenylpropionyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 509: des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 511: des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 517: des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 518: des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 519: des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Phenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2

Compound No. 522: des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 523: des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 524: des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 531: des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 532: des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 533: des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 534: des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 535: des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naphthoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 541: D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 542: D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 545: des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 546: des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 547: des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2
Compound No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 551: Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 552: D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 553: D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 554: D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-β-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 555: D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 556: D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS 10

D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 557: D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tr p10]MS10

D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 559: des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 561: D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 562: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 563: des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 565:

des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2.

Compound No. 566: des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 567: des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 568: Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 569: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH_2NH,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 570: des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 571: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 572: des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 573: des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 580: des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 584: des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 585: des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 589: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 590: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compound No. 591: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compound No. 592: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 594: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compound No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compound No. 596: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compound No. 597: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2
Compound No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 602: des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 603: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2
Compound No. 605: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2
Compound No. 607: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2
Compound No. 608: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2
Compound No. 609: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2
Compound No. 610: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2
Compound No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 612: des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 613: des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 614: des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 619: des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 620: des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 623: des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 631: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 632: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 633: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 634: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 635: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 636: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 637: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 638: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 639: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compound No. 641: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compound No. 642: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 643:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2
Compound No. 644: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2
Compound No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2
Compound No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2
Compound No. 647: des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 649: Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 651: Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 652: des(1)-pGlu-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 653: des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 654: des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 655: des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-MeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 656:

des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-MeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 658: des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 659: des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 660: des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 667: des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 668: des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 669: des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 670:

des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 671: des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 672: des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 674: des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 677: Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2

Compound No. 678: Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2

Compound No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 680: des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glycoloyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 681: des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Glycoloyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 682: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2

Compound No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 686: des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2

Compound No. 689:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2

Compound No. 691:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 692:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 693:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 694:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 695:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 696:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 698:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compound No. 699:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compound No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compound No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 702:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 703:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

However, the metastin derivatives (III) of the present invention do not include a peptide (native human metastin or its partial peptides) consisting of the following amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1, i.e., the amino acid sequence of 1-54 (Compound No. 1), 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54 (Compound No. 2), 41-54, 42-54 (Compound No. 32), 43-54, 44-54, 45-54 (Compound No. 3), 46-54 (Compound No. 4), 47-54, 48-54 or 49-54.

In the metastin derivatives (II), all compounds that the groups shown by the respective symbols are optionally combined are preferably used. Among them, the compounds shown by Compound Numbers below are preferred.

Compound No. 332: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10
GuAmb-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 333: des(1-5)-GuAmb-[Arg(Me)9]MS10
GuAmb-Phe-Gly-Leu-Arg(Me)-Phe-NH_2
Compound No. 334: des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10
GuAmb-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 339: des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10
3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 340: des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10
3-(3-Pyridyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 341: des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9]MS10
Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 344: des(1-5)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10
Indole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 345: des(1-5)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10
Indole-3-acetyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 346: des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10
Ac-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 347: des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10
n-Hexanoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 348: des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10
Z-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 349: des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10
Tos-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 351: des(1-5)-Benzoyl-MS10
Benzoyl-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 352: des(1-5)-3-(3-Indolyl)propionyl-MS10
3-(3-Indolyl)propionyl-Phe-Gly-Leu-Arg-Phe-NH_2
Compound No. 353: des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 354: des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
3-(3-Indolyl)propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 358: des(1-5)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 362: des(1-6)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10
3-Phenylpropionyl-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 364: des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10
2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 366: des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
n-Hexanoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 367: des(1-5)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10
Z-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 368: des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10
Tos-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 369: des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
2-(Indol-3-yl)ethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 373:

des(1-6)-(2S)-2-acetoxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
(2S)-2-acetoxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 374: des(1-6)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10
Z-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 378: des(1-6)-Diphenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Diphenylacetyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 379: des(1-6)-(2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
(2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 380: des(1-6)-(2S)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
(2S)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 392: des(1-5)-Benzoyl-[Ala6,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 393: des(1-6)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Dibenzylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 408: des(1-6)-1-Oxo-isochroman-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10
1-Oxo-isochroman-3-carbonyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 412: des(1-6)-(2R)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
(2R)-2-Benzoyloxy-3-phenylpropionyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 417: des(1-6)-Benzylphenethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Benzylphenethylcarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 421: des(1-5)-Benzoyl-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10
Benzoyl-PheΨ(CH2O)Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 423: des(1-5)-Benzoyl-[6Ψ7,NHCO,Arg(Me)9,Trp10]MS10
Benzoyl-PheΨ(NHCO)Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 428: des(1-6)-Dibenzylaminocarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Dibenzylaminocarbamoyl-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 431: des(1-5)-Benzoyl-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-AzaPhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 432: des(1-5)- 3-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 434: des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10

Dibenzylaminocarbamoylacetyl-Leu-Arg(Me)-Trp-NH_2

Compound No. 435: des(1-5)-2-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 436: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 437: des(1-5)-Propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Propionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 438: des(1-5)-Isobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10

Isobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 439: des(1-5)-Cyclohexanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 440: des(1-5)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Phenylacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 441: des(1-5)-Benzoyl-[Pya(2)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Pya(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 442: des(1-5)-Benzoyl-[Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 443: des(1-5)-2-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 444: des(1-5)-5-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

5-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 445: des(1-5)-6-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Methylnicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 446: des(1-5)-Pyrazinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrazinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 447: des(1-5)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 448: des(1-5)-Trifluoroacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Trifluoroacetyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 449: des(1-5)-Benzoyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 450: des(1-5)-Benzyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Benzyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 451: des(1-5)-Cyclopropanecarbonyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 452: des(1-5)-(R)-3-hydroxy-2-methylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10

(R)-3-hydroxy-2-methylpropionyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 453: des(1-5)-2-Hydroxyisobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Hydroxyisobutyryl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 454: des(1-5)-3-Furancarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

3-Furancarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 455: des(1-5)-Pyrrole-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrrole-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 459: des(1-5)-4-Imidazolecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Imidazolecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 460: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 461: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Nal(2)10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 462: des(1-5)-6-Hydroxynicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Hydroxynicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 463: des(1-5)-6-Chloronicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-Chloronicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 464: des(1-5)-6-(Trifluoromethyl)nicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

6-(Trifluoromethyl)nicotinoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 466: des(1-5)-2-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 467: des(1-5)-Dimethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Dimethylcarbamoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 468: des(1-5)-1-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

1-Azetidinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 471: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 472: des(1-5)-4-Aminobenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminobenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 473: des(1-5)-4-Aminomethylbenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

4-Aminomethylbenzoyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 474: des(1-5)-Pyrrole-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrrole-3-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 475: des(1-5)-Pyrimidine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrimidine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 477: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Orn9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 478: des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Har9,Trp10]MS10

4-Pyridinecarbonyl-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 479: des(1-5)-Pyrimidine-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyrimidine-2-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 480: des(1-5)-Pyridazine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Pyridazine-4-carbonyl-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 481: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 486: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Orn-Phe-NH_2

Compound No. 487: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Lys-Phe-NH_2

Compound No. 488: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har-Phe-NH_2

Compound No. 489: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Har(Me)-Phe-NH_2

Compound No. 490: des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10

D-Tyr-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 491: des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Trp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 492: des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 493: des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 494: des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 495: des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-Pya(4)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 496: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 497: des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Cha-Ala-Leu-Arg(Me)-Trp-NH_2
Compound No. 498: des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 499: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 500: des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 501: des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 502: des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-Pya(4)-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 503: des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 504: [Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10
Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 505: des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 506: des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ile-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 507: des(1-3)-3-Phenylpropionyl-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 508: des(1-3)-3-Phenylpropionyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 509: des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 510: des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 511: des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Ala-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 512: des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 513: des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 514: des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Phe-Ala-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 515: des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10
D-Tyr-D-Pya(4)-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 516: des(1)-Ac-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10
Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 517: des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 518: des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10
3-Phenylpropionyl-Asn-Ser-Cha-Gly-Leu-Arg(Me)-Trp-NH_2
Compound No. 519: des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10
Phenylacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 521: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg-Phe-NH_2
Compound No. 522: des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Benzoyl-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 523: des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 524: des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 527: des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Hyp-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 528: des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 529: des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Tle-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 530: des(1)-[D-Tyr2,D-Pya(4)3,Phg5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Phg-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 531: des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Pic(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 532: des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 533: des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-D-Pro-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 534: des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 535: des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10

2-Naphthoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 536: [Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 537: Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Arg-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 538: Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

Arg-Acp-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 539: des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 540: des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 541: D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 542: D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 545: des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 546: des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Phenylpropionyl-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 547: des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Ser(Ac)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 548: des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10

D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2

Compound No. 550: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 551: Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 552: D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 553: D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 554: D-Arg-[β-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-β-Ala-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 555: D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 556: D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 557: D-Arg-D-Arg-D-Arg-[γ-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-D-Arg-D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 558: des(1)-Ac-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 559: des(1-2)-3-(4-Hydroxyphenyl)propionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 561: D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

D-Arg-Acp-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 562: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 563: des(1)-Ac-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Aze(2)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 564: des(1)-Ac-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 565: des(1)-Benzoyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 566: des(1)-Cyclopropanecarbonyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 567:

des(1)-Butyryl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 568: Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Arg-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 569: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH_2NH,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-PheΨ(CH_2NH)Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 570: des(1)-Me-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Me-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 571: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2

Compound No. 572: des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 573: des(1)-Ac-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Abu-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 576: des(1)-Ac-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Gln-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 577: des(1)-Ac-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Ser-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 578: des(1)-Ac-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Thr-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 579: des(1)-Ac-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 580: des(1)-Ac-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 584: des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 585: des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 586: des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 589: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2

Compound No. 590: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi(2)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2

Compound No. 591: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2

Compound No. 592: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2

Compound No. 594: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Hph-NH_2

Compound No. 595: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Cha10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Cha-NH_2

Compound No. 596: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Leu10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Leu-NH_2

Compound No. 597: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 598: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 599: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2

Compound No. 600: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2

Compound No. 601: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-D-Phe-Gly-Leu-Arg(Me)-Trp-NH_2

Compound No. 602: des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 603: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-D-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 604: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Tos)-Trp-NH_2

Compound No. 605: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(NO2)-Trp-NH_2

Compound No. 607: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)asym-Trp-NH_2

Compound No. 608: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me2)sym-Trp-NH_2

Compound No. 609: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Et)-Trp-NH_2

Compound No. 610: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys(Me2)-Trp-NH_2

Compound No. 611: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 612: des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 613: des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 614: des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Amidino-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 615: des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 616: des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 617: des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 618: des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 619: des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(1)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 620: des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Nal(2)-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 621: des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 622: des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Glu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 623: des(1)-Ac-[D-Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 624: des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 625: des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 626: des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 627: des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 628: des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Thr-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 629: des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 630: des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 631: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Ala-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 632: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Leu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 633: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Lys-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 634: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Glu-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 635: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 636: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,NMePhe6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-MePhe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 637: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 638: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 639: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Lys-Trp-NH_2

Compound No. 641: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ala-Arg(Me)-Trp-NH_2

Compound No. 642: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2

Compound No. 643: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Phe-Arg(Me)-Trp-NH_2

Compound No. 644: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ser-Arg(Me)-Trp-NH_2

Compound No. 645: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har-Trp-NH_2

Compound No. 646: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Har(Me)-Trp-NH_2

Compound No. 647: des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asp-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 648: [Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 649: Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 650: [D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 651: Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 652: pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 653: des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-D-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 654: des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-D-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 655: des(1)-Ac-[D-Tyr2,D-Trp3,NMeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-NMeAsn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 656: des(1)-Ac-[D-Tyr2,D-Trp3,NMeSer5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-NMeSer-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 657: des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 658: des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 659: des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Trp-Asn-allo-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 660: des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 661: des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-D-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 662: des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 663: des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 664: des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 665: des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 666: des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 667: des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 668: des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Cyclohexanecarbonyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 669: des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Benzoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 670: des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 671: des(1-2)-Adipoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No.: des(1)-Ac-[D-Tyr2,NMeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10

Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 674 :
des(1-2)-6-Aminocaproyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 675: [D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 676: Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 677:
Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Nva-Arg(Me)-Trp-NH_2
Compound No. 678:
Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Ile-Arg(Me)-Trp-NH_2
Compound No. 679: des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Amidino-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 680:
des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Glycoloyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 681:
des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Glycoloyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 682:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Gln-Arg(Me)-Trp-NH_2
Compound No. 685: des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2
Compound No. 686: des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Gly-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2
Compound No. 688: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Pya(4)-Trp-NH_2
Compound No. 689:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-D-Trp-NH_2
Compound No. 691:

des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Tyr-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 692:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Trp-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 693:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Tyr(Me)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 694:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Nal(2)-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 695:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Thi-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 696:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Cha-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 698:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Abu-Arg(Me)-Trp-NH_2

Compound No. 699:
des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-γMeLeu-Arg(Me)-Trp-NH_2

Compound No. 700: des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-Gly-Aib-Arg(Me)-Trp-NH_2

Compound No. 701: des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Dap-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 702:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NHMe)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

Compound No. 703:
des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NMe2)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10
Ac-D-Tyr-D-Trp-Asp(NMe2)-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

For metastin derivatives (II), preferably used are metastin derivatives represented by the formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl (e.g., acetyl, propionyl, butyryl, hexanoyl, and so on; preferably acetyl, propionyl, butyryl; more preferably acetyl), cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, or 3-(4-Hydroxyphenyl)propionyl, glycyl. tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl (preferably acetyl and the like);

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm (preferably D-Tyr or bond arm; more preferably D-Tyr);

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine (preferably D-Trp or D-4-pyridylalanine);

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid (preferably Asn);

XX5 represents Ser, Thr or Val (preferably Ser or Thr);

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4-pyridylalanine or 4-fluorophenylalanine (preferably Phe or 4-fluorophenylalanine);

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val (prerferably Leu);

XX9 represents Arg, OrnArg(Me), or Arg(symMe2) (preferably Arg(Me));

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine (preferably Phe or Trp)), or a salt thereof. Further, compounds represented by the following compound number are preferred:

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),

Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),

D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),

Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),

3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compound No. 559),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),

Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),

Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),

For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),

Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),

Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),

Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),

Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),

Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),

Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),

Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663), or salts thereof.

The metastin derivatives (II) of the present invention or their salts or prodrugs have excellent blood stability, in addition to excellent effects of suppressing cancer metastasis and cancer growth, and are useful as agents for preventing or treating cancers (for example, lung cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, etc.). The metastin derivatives (II) of the present invention or their salts or prodrugs have an effect of controlling pancreatic function and are useful as agents for

preventing or treating pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.). The metastin derivatives (II) of the present invention or their salts or prodrugs have an effect of controlling placental function and are useful as agents for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

Moreover, the metastin derivatives (II) of the present invention or their salts or prodrugs have effects of increasing sugar level, promoting pancreatic glucagon secretion and promoting urine formation, and are useful as agents for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

In addition, the metastin derivatives (II) of the present invention or their salts or prodrugs have excellent activities of promoting gonadotropic hormone secretion, promoting sex hormone secretion, inducing ovulation or stimulating ovulation, and are useful as low toxic and stable agents, e.g., agents for improving gonadal function, agents for preventing or treating hormone-dependent cancer (e.g., prostate cancer, breast cancer, etc.), infertility, endometriosis, early puberty, myoma of the uterus, etc., agents for inducing or stimulating ovulation, gonadotropic hormone secretagogue agents, contraceptives, sex hormone secretagogue agents, or the like.

Furthermore, the metastin derivatives (II) of the present invention or their salts or prodrugs are useful as agents for preventing or treating Alzheimer's disease, moderate cognitive impairment, etc.

The metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone or sex hormone; down-regulating agents for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer, breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for

treating early puberty; contraceptives, etc.

In addition, the metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as an agent for potentiating immunity (prophylactic agent for infection after bone-marrow transplant, an agent for potentiating immunity intended for cancer); a prophylactic/therapeutic agent for bulbospinal muscular atrophy; an agent for protecting ovary; a prophylactic/therapeutic agent for benign prostate hypertrophy (BPH); a prophylactic/therapeutic agent for gender identity disorder; or an agent for in vitro fertilization (IVF). In addition, it is useful as a prophylactic/therapeutic agent for infertility, hypogonadism, oligospermia, azoospermia, aspermia, asthenospermia, or necrospermia. Further, it is useful for hormone-dependent diseases such as prostate cancer, uterine cancer, breast cancer, sex hormone dependent cancer like hypohysial tumor, prostate gland enlargement, endometriosis, uterine fibroid, early puberty, dysmenorrhea, amenorrhea, menstrual syndrome, multilocular ovary syndrome, postoperative relapse of the above-mentioned cancers, metastasis of the above-mentioned cancers, hypopituitarism, dwarfism (the case where the secretion of growth hormone was compromised associating with hyposecretion of pituitary hormone), menopausal disorder, indefinite complaint, sex hormone dependent disorders such as calcium phosphor bone metabolic disorders. It is applicable for contraception (or infertility when rebound effects after cessation of the drug are utilized).

Furthermore, metastin per se, DNA encoding metastin, etc. are also useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone or sex hormone; down-regulating agents for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer, breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for treating early puberty; contraceptives, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

The metastin derivatives (I) and (II) of the present invention can be prepared by publicly known methods for peptide synthesis. As the methods for peptide synthesis,

for example, either solid phase synthesis or liquid phase synthesis may be used. That is, the partial peptide or amino acids that can constitute the peptide of the present invention are repeatedly condensed with the remaining part to give the product having a desired sequence. Where the product has protecting groups, these protecting groups are removed to give the desired peptide. Publicly known methods for condensation and removal of the protecting groups are described in (i) to (v) below.

(1) M. Bodanszky & M.A. Ondetti: Peptide Synthesis, Interscience Publishers, New York (1966)

(2) Schroeder & Luebke: The Peptide, Academic Press, New York (1965)

(3) Nobuo Izumiya, et al.: *Peptide Gosei-no-Kiso to Jikken* (Basics and experiments of peptide synthesis), published by Maruzen Co. (1975)

(4) Haruaki Yajima & Shunpei Sakakibara: *Seikagaku Jikken Koza* (Biochemical Experiment) 1, *Tanpakushitsu no Kagaku* (Chemistry of Proteins) IV, 205 (1977)

(5) Haruaki Yajima, ed.: *Zoku Iyakuhin no Kaihatsu* (A sequel to Development of Pharmaceuticals), Vol. 14, Peptide Synthesis, published by Hirokawa Shoten

After completion of the reaction, the product may be purified and isolated by a combination of conventional purification methods such as solvent extraction, distillation, column chromatography, liquid chromatography and recrystallization to give the partial peptide of the present invention. When the peptide obtained by the above methods is in a free form, the peptide can be converted into an appropriate salt by a publicly known method; when the protein is obtained in a salt form, it can be converted into its free form by publicly known methods.

For condensation of the protected amino acids or peptides, a variety of activation reagents for protein synthesis may be used, but trisphosphonium salts, tetramethyluronium salts, carbodiimides, etc. are particularly preferred. Examples of trisphosphonium salts include benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), bromotris(pyrrolidino) phosphonium hexafluorophosphate (PyBroP) and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP), examples of tetramethyluronium salts include 2-(1H-benzotriazol-1-yl)-1,1,3,3-hexafluorophosphate (HBTU), 2-(7-azabenzotriazol-1-yl)-1,1,3,3-hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetraflluoroborate (TBTU),

2-(5-norbornene-2,3-dicarboxyimido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU) and O-(N-succimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU); examples of carbodiimides include DCC, N,N'-diisopropylcarbodiimide (DIPCDI) and N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI.HCl); etc. For condensation using these reagents, the addition of racemization inhibitors (e.g., HONB, HOBt, HOAt, HOOBt, etc.) is preferred. Solvents used in condensation may be appropriately chosen from solvents that are known to be usable for condensation. For example, acid amides such as anhydrous or hydrous N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, etc., halogenated hydrocarbons such as methylene chloride, chloroform, etc., alcohols such as trifluoroethanol, phenol, etc., sulfoxides such as dimethyl sulfoxide, etc., tertiary amines such as pyridine, etc., ethers such as dioxane, tetrahydrofuran, etc., nitriles such as acetonitrile, propionitrile, etc., esters such as methyl acetate, ethyl acetate, etc., or suitable mixtures thereof, etc. are used. The reaction temperature is appropriately chosen from the range known to be applicable to peptide binding reactions and is normally suitably chosen from the range of about -20°C to 50°C. The activated amino acid derivatives are used generally in 1.5 to 6 times excess. In the case of solid phase synthesis, the condensation is examined using the ninhydrin reaction; when the condensation is insufficient, the condensation can be completed by repeating the condensation reaction without removal of the protecting groups. When the condensation is yet insufficient even after repeating the reaction, the unreacted amino acids are acylated with acetic anhydride or acetylimidazole to cancel any adverse effect on the subsequent reaction.

Examples of the protecting groups used to protect amino groups in the starting amino acids include Z, Boc, tert-pentyloxycarbonyl, isobornyloxycarbonyl, 4-methoxybenzyloxycarbonyl, Cl-Z, Br-Z, adamantyloxycarbonyl, trifluoroacetyl, phthaloyl, formyl, 2-nitrophenylsulphenyl, diphenylphosphinothioyl, Fmoc, trityl, etc. Examples of protecting groups for a carboxyl group include, in addition to the C_{1-6} alkyl group, C_{3-8} cycloalkyl group and C_{7-14} aralkyl group for R described above, allyl, 2-adamantyl, 4-nitrobenzyl, 4-methoxybenzyl, 4-chlorobenzyl, phenacyl group, benzyloxycarbonylhydrazide, tert-butoxycarbonylhydrazide, tritylhydrazide, etc.

The hydroxyl group of serine and threonine can be protected, for example, by esterification or etherification. Examples of groups suitable for this esterification include a lower (C_{2-4}) alkanoyl group such as acetyl group, an aroyl group such as benzoyl group, etc. and a group derived from organic acid. Examples of a group suitable

for the etherification include benzyl group, tetrahydropyranyl group, tert-butyl group, trytyl group (Trt), etc.

Examples of groups for protecting the phenolic hydroxyl group of tyrosine include Bzl, Cl_2-Bzl, 2-nitrobenzyl, Br-Z, tert-butyl, etc.

Examples of groups used to protect the imidazole moiety of histidine include Tos, 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), DNP, Bom, Bum, Boc, Trt, Fmoc, etc.

Examples of protecting groups for a guanidino group of arginine include Tos, Z, 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), p-methoxybenzenesulfonyl (MBS), 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc), mesitylene-2-sulfonyl (Mts), 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), Boc, Z, NO_2, etc.

Examples of protecting groups for side chain amino group of lysine include Z, Cl-Z, trifluoroacetyl, Boc, Fmoc, Trt, Mtr, 4,4-dimethyl-2,6-dioxocyclohexylideneyl (Dde), etc.

Examples of protecting groups for indolyl of tryptophan include formyl (For), Z, Boc, Mts, Mtr, etc.

A protecting group for asparagine and glutamine include Trt, xanthyl (Xan), 4,4'-dimethoxybenzhydryl (Mbh), 2,4,6-trimethoxybenzyl (Tmob), etc.

Examples of the activated carboxyl groups in the starting material include the corresponding acid anhydrides, azides, activated esters [esters with alcohols (e.g., pentachlorophenol, 2,4,5-trichlorophenol, 2,4-dinitrophenol, cyanomethyl alcohol, p-nitrophenol, HONB, N-hydroxysuccimide, 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt)], etc. As the amino acids in which the amino groups in the starting material are activated, the corresponding phosphoric amides are employed.

To eliminate (split off) the protecting groups, there are used catalytic reduction under hydrogen gas flow in the presence of a catalyst such as Pd-black or Pd-carbon; an acid treatment with anhydrous hydrogen fluoride, methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, trimethylsilane bromide (TMSBr), trimethylsilyl trifluoromethanesulfonate, tetrafluoroboric acid, tris(trifluoro)boron, boron tribromide or a mixed solution thereof, a base treatment with diisopropylethylamine, triethylamine, piperidine, piperazine, etc., and reduction with sodium in liquid ammonia. The elimination of protecting groups by the acid treatment described above is carried out generally at a temperature of approximately -20°C to

40°C. In the acid treatment, it is efficient to add a cation scavenger such as anisole, phenol, thioanisole, m-cresol, p-cresol, etc., dimethylsulfide, 1,4-butanedithiol, 1,2-ethanedithiol, etc. Furthermore, 2,4-dinitrophenyl group known as the protecting group for the imidazole of histidine is removed by a treatment with thiophenol. Formyl group used as the protecting group of the indole of tryptophan is removed by the aforesaid acid treatment in the presence of 1,2-ethanedithiol, 1,4-butanedithiol, etc. as well as by a treatment with an alkali such as a dilute sodium hydroxide solution, dilute ammonia, etc.

Protection of functional groups that should not be involved in the reaction of the starting materials, protecting groups, removal of the protecting groups and activation of functional groups involved in the reaction may be appropriately chosen from publicly known groups and publicly known means.

In another method for obtaining the amides of the peptide, for example, the α-carboxyl group of the carboxy terminal amino acid is first protected by amidation; the peptide chain is then extended from the amino group side to a desired length. Thereafter, a peptide in which only the protecting group of the N-terminal α-amino group in the peptide chain has been removed from the peptide and a peptide (or an amino acid) in which only the protecting group of the C-terminal carboxyl group has been eliminated are prepared. The two peptides are condensed in a mixture of the solvents described above. The details of the condensation reaction are the same as described above. After the protected peptide obtained by the condensation is purified, all the protecting groups are removed by the method described above to give the desired crude peptide. This crude peptide is purified by various known purification means. Lyophilization of the major fraction gives the amide of the desired peptide.

When the metastin derivatives (I) and (II) of the present invention are present as a configurational isomer, a diastereomer, a conformer or the like, each can be isolated by the separating and purifying means described above, if desired. In addition, when the compound of the present invention is racemic, it can be separated into an S isomer and an R isomer by the conventional optical resolving means.

When the metastin derivatives (I) and (II) of the present invention have steric isomers, the present invention includes both of these isomers alone and the isomers present as a mixture thereof.

In addition, the metastin derivatives (I) and (II) of the present invention may be hydrated or non-hydrated.

The metastin derivatives (I) and (II) of the present invention may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S), etc.

Throughout the present specification, the peptides are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at the left hand and the C-terminus (carboxyl terminus) at the right hand. In the peptides, the C-terminus is usually in the form of an amide ($-CONH_2$), a carboxyl group (-COOH), a carboxylate ($-COO^-$), an alkylamide (-CONHR) or an ester (-COOR) and the amide ($-CONH_2$) is particularly preferred. Examples of the ester or alkylamide as R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl group such as a phenyl-C_{1-2}-alkyl group, e.g., benzyl, phenethyl, etc., or an α-naphthyl-C_{1-2}-alkyl group such as α-naphthylmethyl, etc.; pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Examples of a salt of the metastin derivative (I) of the present invention include a metal salt, a salt with ammonium, a salt with an organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid, and the like. Preferred examples of the metal salt include alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts, etc.; aluminum salts; and the like. Preferred examples of the salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred examples of the salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferred examples of salts with acidic amino acids include salts with aspartic, glutamic acid, etc.

Among them, pharmaceutically acceptable salts are preferable. For example, when the compound has an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g., calcium salt,

magnesium salt, barium salt, etc.), ammonium salts, etc. are preferable. When the compound has a basic functional group, salts with inorganic acids with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc., and salts with organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. are preferable.

A prodrug of the metastin derivative (III) or a salt thereof (hereinafter sometimes simply referred to as the metastin derivative (III) of the present invention) means a metastin derivative that is converted into the metastin derivative (III) of the present invention under physiological conditions or with a reaction due to an enzyme, a gastric acid, etc., in the living body. That is, the prodrug of the present invention is a metastin derivative that undergoes enzymatic oxidation, reduction, hydrolysis, etc. to be converted into the metastin derivative (III) of the present invention, or a metastin derivative that undergoes hydrolysis, etc. by gastric acid, etc. to be converted into the metastin derivative (III) of the present invention.

The prodrugs of the metastin derivative (I) of the present invention or salts thereof (hereinafter sometimes simply referred to as the metastin derivative (I) of the present invention) and the prodrugs of the metastin derivative (II) of the present invention or salts thereof (hereinafter sometimes simply referred to as the metastin derivative (II) of the present invention), which can be used, are the same as those described for the prodrugs of the metastin derivative (III) of the present invention.

Examples of the prodrugs of the metastin derivatives (III) of the present invention include metastin derivatives wherein an amino group of the metastin derivative (III) of the present invention is substituted with an acyl, an alkyl, phosphoric acid, etc. (e.g., metastin derivatives wherein an amino group of the metastin derivative (III) of the present invention is substituted with eicosanoyl, alanyl, pentylaminocarbonyl (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc); metastin derivatives wherein a hydroxy group of the metastin derivative (I) of the present invention is substituted with an acyl, an alkyl, phosphoric acid, boric acid, etc. (e.g., metastin derivatives wherein an hydroxy group of the metastin derivative (III) of the present invention is substituted with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); and metastin derivatives wherein a carboxyl group of the metastin derivative (III) of the present invention is substituted with ester, amide,

etc. (e.g., metastin derivatives wherein a carboxyl group of the metastin derivative (III) of the present invention is substituted with ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methylamide, etc); and the like. These metastin derivatives can be produced from the metastin derivative (I) of the present invention by per se known methods.

The prodrugs of the metastin derivative (III) of the present invention may be those that are converted into the metastin derivative (III) of the present invention under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pages 163-198, published 1990 by Hirokawa Publishing Co.

The metastin derivatives (I), (II) or (III) of the present invention or their salts or prodrugs (hereinafter sometimes simply referred to as the compound of the present invention) possess a cancer metastasis suppressing activity or a cancer growth suppressing activity. Thus, the metastin derivatives are useful for pharmaceuticals such as agents for preventing or treating all cancers (e.g., lung cancer, gastric cancer, liver cancer, pancreas cancer, colorectal cancer, rectal cancer, colonic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, etc.).

The compounds of the present invention also possess the effect of controlling pancreatic function and are thus useful as agents for preventing or treating various pancreatic diseases (e.g., acute or chronic pancreatitis, pancreatic cancer, etc.) as agents for controlling pancreatic function.

The compounds of the present invention also possess the effect of controlling placental function and are thus useful as pharmaceuticals for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, as agents for controlling placental function.

Furthermore, the compounds of the present invention possess the effects of increasing sugar level, promoting pancreatic glucagon secretion and promoting urine formation and are thus useful as pharmaceuticals such as hyperglycemic agents, pancreatic glucagon secretagogue agents or agents for promoting urine formation, which are useful for preventing or treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy,

diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.

In addition, the compounds of the present invention also possess the effects of promoting gonadotropic hormone (e.g., FSH, LH, etc.) secretion, promoting sex hormone [e.g., androgens (e.g., testosterone, androstenedione, etc.), estrogens (e.g., estradiol, estrone, etc.), progesterones, etc.] secretion, improving gonadal function and inducing or stimulating ovulation, as well as a sexual maturation effect, etc., and hence, can be used as agents for improving gonadal function, agents for inducing or stimulating ovulation, gonadotropic hormone secretagogue agents or sex hormone secretagogue agents, or agents for preventing or treating hormone-dependent cancers [e.g., prostate cancer, breast cancer, etc.], infertility [e.g., irregular menstruation, dysmenorrhea, amenorrhea, weight loss-induced amenorrhea, secondary amenorrhea, anovulation, hypoovarianism, hypogonadism, spermatogenetic failure, hypogonadism (e.g., impotence, etc.), genital atrophy, testicular atrophy, testicular function disorder, azoospermia, hypoandrogenemia, etc.], endometriosis, early puberty, myoma of the uterus, etc.

Furthermore, the prodrugs of the metastin derivative (I) or (II) of the present invention or salts thereof are useful as agents for preventing or treating Alzheimer's disease, moderate cognitive impairment, etc.

Moreover, the compounds of the present invention have excellent blood stability, as compared to native metastin such as metastin 54 (1-54) or metastin 10 (45-54).

The metastin derivatives (III) [including the metastin derivatives (II) and the metastin derivatives (I)] of the present invention or their salts or prodrugs are useful as agents for suppressing gonadotropic hormone secretion or sex hormone secretion; down-regulating agents for gonadotropic hormone (e.g., FSH, LH) or sex hormone [e.g., androgen (e.g., testosterone, androstenedione), estrogen (e.g., estradiol, estorone), progesterone];in particular, it is useful for suppressing gonadotropic hormone secretion or sex hormone secretion via down-regulation of gonadotropic hormone or sex hormone (wherein, the down-regulation of gonadotropic hormone or sex hormone may be pulse loss of LHRH or depletion of LHRH) or down-regulation of human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9; as agents for preventing or treating hormone-dependent cancers (e.g., prostate cancer,

breast cancer, etc.; particularly, hormone-sensitive prostate cancer, hormone-sensitive prostate cancer, etc.); agents for preventing or treating endometriosis; agents for inhibiting ovarian follicular maturation; menstrual cycle-suspending agents; agents for treating myoma of the uterus; agents for treating early puberty; or as contraceptives, etc.

Where the metastin derivative (III) of the present invention [including the metastin derivative (II) and the metastin derivative (I)] or its salt or prodrug, metastin per se, or DNA encoding metastin, etc. have normal agonist activity, an effective dose of the metastin derivative sufficient to suppress the secretion of gonadotropic hormone or sex hormone is administered at the site or tissue where the therapeutic effects are to be exerted, so that the metastin derivative is present in a dose more than required (i.e., the metastin derivative is administered in an excess over the normal effective dose, at which the metastin derivative exerts the effects of suppressing cancer metastasis, suppressing cancer growth, etc.; or the gonadotropic hormone secretagogue agent, the effect of promoting sex hormone secretion, etc.) to exhibit the effects of suppressing gonadotropic hormone secretion or sex hormone secretion. Specific examples include sustained or continuous administration of the normal effective dose (including an administration technique to gradually release the pharmaceutical ingredients by bolus administration); and the like. Further when the metastin derivative (III) of the present invention [including the metastin derivative (II) and the metastin derivative (I)] or its salt or the prodrug thereof, etc. have a sufficient agonist activity more than required (a super-agonist activity), it becomes possible to sustain the activities more than exhibited by the necessary dose at the site or tissue where the therapeutic effect are to be exhibited. It is therefore sufficient even by normal effective dose administration to suppress the secretion of gonadotropic hormone or sex hormone, whereby the effect of suppressing gonadotropic hormone secretion or sex hormone secretion is exhibited.

That is, the metastin derivative (III) [including the metastin derivative (II) and the metastin derivative (I)] or its salt or prodrug, or metastin per se, metastin-encoding DNA, etc. are administered in an effective dose sufficient to suppress the secretion of gonadotropic hormone or sex hormone. Consequently, it becomes possible to keep the metastin derivative, etc. present in a dose more than the necessary dose or sustain the activity more than exhibited by the necessary dose, at the site or tissue where the pharmaceutical effects are to be exhibited, resulting in exerting the effect of suppressing gonadotropic hormone secretion or sex hormone secretion.

The pharmaceutical compositions comprising the compounds of the present

invention are low toxic and thus can be safely administered orally or parenterally (e.g., topically, rectally, intravascularly, etc.) either directly as they are or in the form of pharmaceutical preparations such as tablets (including dragees and film-coated tablets), powdery dosage forms, granules, capsules (including soft capsules), liquid dosage forms, injections, suppositories, sustained release dosage forms, etc.

The compound of the present invention is contained in the pharmaceutical preparation of the present invention in about 0.01 to about 100 wt%, based on the total weight of the preparation.

A dose of the compound of the present invention may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in oral administration, the compound is generally administered to the patient with cancer (as 60 kg body weight) in a daily dose of about 0.1 to about 100 mg, preferably about 1.0 to about 50 mg and more preferably about 1.0 to about 20 mg. In parenteral administration, a single dose of the compound may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in the form of an injectable dosage form, it is advantageous to administer the compound to the patient with cancer (as 60 kg body weight) generally in a daily dose of about 0.01 to about 30 mg, preferably about 0.1 to about 20 mg, and more preferably about 0.1 to about 10 mg. For other animal species, the corresponding dose as converted per 60 kg weight can be administered.

Pharmacologically acceptable carriers, which may be used in manufacturing the pharmaceutical preparation of the present invention, include various organic or inorganic carrier substances conventionally used as materials for pharmaceutical preparations. These substances include, e.g., an excipient, a lubricant, a binder and a disintegrating agent in a solid dosage form, and a solvent, a dissolution aid, a suspending agent, an isotonizing agent, a buffer, a soothing agent, etc. in a liquid dosage form. In addition, conventional additives such as a preservative, an antioxidant, a colorant, a sweetener, an adsorbent, a wetting agent, etc. can be appropriately used in suitable amounts, if necessary.

Examples of excipients include, e.g., lactose, saccharose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

Examples of useful lubricants include, e.g., magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Examples of binders include, e.g., crystalline cellulose, saccharose,

D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethylcellulose, etc.

Examples of disintegrating agents include, e.g., starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose, etc.

Examples of solvents include, e.g., water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil, etc.

Examples of dissolution aids include, e.g., polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Examples of suspending agents include, e.g., surfactants such as stearyltriethanolamine, sodium laurylsulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerine monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

Examples of isotonizing agents include, e.g., glucose, D-sorbitol, sodium chloride, glycerine, D-mannitol, etc.

Examples of buffers include, e.g., buffering solutions of a phosphate, acetate, carbonate, citrate, etc.

Examples of soothing agents include, e.g., benzyl alcohol, etc.

Examples of preservatives include, e.g., p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

Examples of antioxidants include, e.g., a sulfite, ascorbic acid, α-tocopherol, etc.

Furthermore, the compound of the present invention can be used in combination with drugs other than the compound of the present invention.

Examples of the drugs, which can be used in combination with the compound of the present invention (hereinafter referred to as a combination drug), include chemotherapeutic agents for treating cancer, hormonal therapeutic agents, immunotherapeutic agents, etc.

Examples of "chemotherapeutic agents" include, e.g., alkylating agents, antimetabolites, anticancer antibiotics, and plant-derived anticancer agents.

Examples of "alkylating agents" include, e.g., nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, estramustine sodium phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, carboquone, adozelesin, cystemustine, bizelesin, etc.

Examples of "antimetabolites" include, e.g., mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, etc.), aminopterin, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, etc.

Examples of "anticancer antibiotics" include, e.g., actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, etc.

Examples of "plant-derived anticancer agents" include, e.g., etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, etc.

Examples of "hormonal therapeutic agents" include, e.g., fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, etc.), pill dosage forms, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, Leuprorelin, etc.), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, etc.), anti-androgens (e.g., flutamide, bicartamide, nilutamide, etc.), 5α-reductase inhibitors

(e.g., finasteride, epristeride, etc.), adrenocorticohormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, etc.), androgen synthesis inhibitors (e.g., abiraterone, etc.), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, etc.), and among them, LH-RH agonists (e.g., goserelin acetate, buserelin, Leuprorelin, etc.) are preferable.

Examples of "immunotherapeutic agents (BRM)" include, e.g., picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, Corynebacterium parvum, levamisole, polysaccharide K, procodazole, etc.

The combined use of the compound of the present invention and a combination drug results in, for example, the following excellent effects.

(1) The dose of the compound of the present invention can be reduced when compared with the dose when administered alone.

(2) A combination drug with the compound of the present invention can be chosen depending on the condition (mild, severe, etc.) of a patient.

(3) A combination drug, whose functional mechanism is different from that of the compound of the present invention, can be chosen so that a treatment period can be set longer.

(4) A combination drug, whose functional mechanism is different from that of the compound of the present invention, can be chosen so that sustained therapeutic effects can be achieved.

(5) A synergistic effect can be obtained by the combined use of the compound of the present invention and a combination drug.

In addition, the compound of the present invention can reduce values of testosterone to emasculate level immediately after medication. Thus when the combination drug such as LH-RH agonist (e.g., goserelin acetate, buserelin, Leuprorelin etc.; preferably Leuprorelin) uses in combination with the compound of the present invention, the values of testosterone can be reduced to emasculate level immediately after medication of the compound of the present invention. Further, since the combined use of the combination drug such as LH-RH agonist (e.g., goserelin acetate, buserelin, Leuprorelin etc.; preferably Leuprorelin) and the compound of the present invention results in prolonged preservation of hormone-dependent period, it can advantageously be used.

Hereinafter, the combined use of Compound (I) of the present invention and a combination drug is referred to as "the combined preparation of the present invention."

When the combined preparation of the present invention is used, a dosing period of the compound of the present invention and the combination is not restricted; the compound of the present invention or its pharmaceutical composition and a combination drug or its pharmaceutical composition may be administered to the subject to be administered either simultaneously or at certain time intervals. The dose of a combination drug may be modified according to the dose used clinically and may be appropriately chosen depending upon subject to be administered, route for administration, disease, combination, etc.

A mode for administration of the combined preparation of the present invention is not particularly limited, but it is sufficient that the compound of the present invention is used in combination with a combination drug at the time of administration. For such mode of administration, there are, for example, (1) administration of a simple dosage form obtained by mixing the compound of the present invention and a combination drug together at the same time, (2) simultaneous administration of two dosage forms prepared separately from the compound of the present invention and a combination drug through the same route for administration, (3) administration of two dosage forms prepared separately from the compound of the present invention and a combination drug at certain time intervals through the same route for administration, (4) simultaneous administration of two dosage forms prepared separately from the compound of the present invention and a combination drug through different routes for administration, (5) administration of two dosage forms prepared separately from the compound of the present invention and a combination drug at certain time intervals (e.g., administration of the compound of the present invention and a combination drug in this order, or administration in a reversed order) through different routes for administration, etc.

The combined preparation of the present invention is low toxic and thus can be safely administered orally or parenterally (e.g., topically, rectally, intravascularly, etc.) either directly as they are or in the form of pharmaceutical preparations such as tablets (including dragees and film-coated tablets), powdery dosage forms, granules, capsules (including soft capsules), liquid dosage forms, injections, suppositories, sustained release dosage forms, etc., which are obtained by mixing the compound of the present invention or (and) a combination drug described above with pharmacologically acceptable carriers. Injectable dosage forms can be administered intravenously,

intramuscularly or subcutaneously, into the organ, or directly at the focus.

Pharmacologically acceptable carriers, which may be used to manufacture the combined preparation of the present invention, include various organic or inorganic carrier substances conventionally used as materials for pharmaceutical preparations. These substances include, e.g., an excipient, a lubricant, a binder and a disintegrating agent in a solid dosage form, and a solvent, a dissolution aid, a suspending agent, an isotonizing agent, a buffer, a soothing agent, etc. in a liquid dosage form. In addition, conventional additives such as a preservative, an antioxidant, a colorant, a sweetener, an adsorbent, a wetting agent, etc. can be appropriately used in suitable amounts, if necessary.

Examples of excipients include, e.g., lactose, saccharose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

Examples of useful lubricants include, e.g., magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Examples of binders include, e.g., crystalline cellulose, saccharose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, sodium carboxymethylcellulose, etc.

Examples of disintegrating agents include, e.g., starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose, etc.

Examples of solvents include, e.g., water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil, etc.

Examples of dissolution aids include, e.g., polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Examples of suspending agents include, e.g., surfactants such as stearyltriethanolamine, sodium laurylsulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerine monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

Examples of isotonizing agents include, e.g., glucose, D-sorbitol, sodium chloride, glycerine, D-mannitol, etc.

Examples of buffers include, e.g., buffering solutions of a phosphate, acetate, carbonate, citrate, etc.

Examples of soothing agents include, e.g., benzyl alcohol, etc.

Examples of preservatives include, e.g., p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

Examples of antioxidants include, e.g., a sulfite, ascorbic acid, α-tocopherol, etc.

In the combined preparation of the present invention, a ratio of the compound of the present invention to a combination drug may be appropriately chosen depending upon subject to be administered, route for administration, disease, combination, etc.

For example, the amount of the compound of the present invention contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, but is usually about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total weight of the preparation.

The amount of a combination drug contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, but is usually about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, and more preferably about 0.5 to 20% by weight, based on the total weight of the preparation.

The amount of additives such as a carrier, etc. contained in the combined preparation of the present invention varies depending on the dosage form of the preparation, and is usually about 1 to 99.99% by weight, preferably about 10 to 90% by weight, based on the total weight of the preparation.

These amounts may be the same, also when the compound of the present invention and a combination drug are separately prepared, respectively.

These preparations can be manufactured by per se publicly known methods generally used conventionally.

For example, an injectable dosage form can be prepared by dissolving, suspending or emulsifying the compound of the present invention or a combination drug in a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder Company, USA), HCO 60 (manufactured by Nikko Chemicals Co., Ltd.), polyethylene glycol, carboxymethyl cellulose, sodium alginate, etc.), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite), a surfactant (e.g., polysorbate 80, macrogol, etc.), a solubilizing agent (e.g., glycerin, ethanol, etc.), a buffering agent (e.g., phosphoric acid or its alkali metal salt,

citric acid or its alkali metal salt, etc.), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose, etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., ethyl p-oxybenzoate, benzoic acid, methylparabene, propylparabene, benzyl alcohol, etc.), a solubilizer (e.g., concentrated glycerin, meglumine, etc.), a dissolution aid (e.g., propylene glycol, saccharose, etc.), a soothing agent (e.g., glucose, benzyl alcohol, etc.), a vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc., a dissolution aid such as propylene glycol or the like to prepare into an oily injection.

An oral dosage form can be produced in a conventional manner by adding to the compound of the present invention or a combination drug, for example, an excipient (e.g., lactose, saccharose, starch, etc.), a disintegrating agent (e.g., starch, calcium carbonate, etc.), a binder (e.g., starch, gum arabic, carboxymethyl cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, etc.), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.) and other additives, compressing the resulting mixture and, if necessary, coating the compressed product for the purpose of taste masking, enteric degradation or sustained release by techniques per se publicly known. Coating agents for this purpose include, for example, hydroxypropylmethyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyoxyethylene glycol, Tween 80, Prulonic F68, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, Eudragit (manufactured by Rohm Company, Germany, methacrylic acid/acrylic acid copolymer) and dyes (e.g., iron oxide, titanium dioxide). The oral dosage form may be either a rapid release dosage form or a sustained release dosage form.

For example, in a suppository, the compound of the present invention or a combination drug is prepared into an oily or aqueous solid, semi-solid or liquid composition by techniques per se publicly known. Oily bases used for the composition described above include glycerides of higher fatty acids [e.g., cacao butter, uitepsols (manufactured by Dynamite Nobel Company, Germany), etc.], moderate fatty acids [e.g., miglyols (manufactured by Dynamite Nobel Company, Germany), etc.], vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.), and the like. Aqueous bases include, for example, polyethylene glycols and propylene glycol. Bases for aqueous gels include, for example, natural rubbers, cellulose derivatives, vinyl polymers, acrylic polymers, etc.

Examples of the sustained release dosage form above include sustained release

microcapsules, and the like.

Sustained release microcapsules can be obtained by per se publicly known methods, and are preferably prepared in the form of, e.g., a sustained release dosage form by the method [2] shown below and administered.

Preferably, the compound of the present invention is prepared into a dosage form for oral administration such as a solid dosage form (e.g., powdery dosage form, granules, tablets, capsules) or into a dosage form for rectal administration such as a suppository, etc. A dosage form for oral administration is particularly preferred.

A combination drug can be prepared into the dosage form described above, depending on the kind of drug.

Hereinafter, [1] an injectable preparation of the compound of the present invention or a combination drug and its production, [2] a sustained release or immediate release preparation of the compound of the present invention or a combination drug and its production and [3] a sublingual, buccal or rapid oral disintegrating preparations of the compound of the present invention or a combination drug and its production will be specifically described.

[1] Injectable Preparation and its Production

An injectable preparation obtained by dissolving the compound of the present invention or a combination drug in water is preferred. The injectable preparation may contain a benzoate and/or a salicylate.

The injectable preparation is obtained by dissolving the compound of the present invention or a combination drug and optionally a benzoate and/or a salicylate in water.

Examples of the benzoate and/or salicylate described above include an alkali metal salt such as sodium and potassium salts, etc., an alkaline earth metal salt such as calcium and magnesium salts, etc., an ammonium salt, a meglumine salt, a salt of an organic acid such as trometamol, and the like.

The concentration of the compound of the present invention or a combination drug in the injectable preparation is about 0.5 to 50 w/v %, preferably about 3 to 20 w/v %. The concentration of the benzoate and/or salicylate is 0.5 to 50 w/v %, preferably 3 to 20 w/v %.

Furthermore, additives generally used in an injectable preparation such as a stabilizer (ascorbic acid, sodium pyrosulfite, etc.), a surfactant (polysorbate 80,

macrogol, etc.), a solubilizing agent (glycerin, ethanol, etc.), a buffering agent (phosphoric acid and its alkali metal salt, citric acid and its alkali metal salt, etc.), an isotonizing agent (sodium chloride, potassium chloride, etc.), a dispersing agent (hydroxypropylmethyl cellulose, dextrin), a pH adjusting agent (hydrochloric acid, sodium hydroxide, etc.), a preservative (ethyl p-oxybenzoate, benzoic acid, etc.), a solubilizer (concentrated glycerin, meglumine, etc.), a dissolution aid (propylene glycol, saccharose, etc.), a soothing agent (glucose, benzyl alcohol, etc.) are appropriately added to the preparation. Any of these additives is added in an amount generally used in an injectable preparation.

The injectable preparation is adjusted to pH of 2 to 12, preferably 2.5 to 8.0 by adding a pH adjusting agent.

The injectable preparation is obtained by dissolving both the compound of the present invention or a combination drug and optionally a benzoate and/or salicylate, and, if necessary, the above additives in water. These components may be dissolved in any order according to the same manner as in a conventional injectable preparation.

An aqueous solution for injection is preferably warmed, and used as an injectable preparation after filtration sterilization by filtration or autoclaved as in a conventional injectable preparation to provide for an injectable preparation.

An aqueous injectable preparation is preferably autoclaved, e.g:, at 100 to 121°C for 5 to 30 minutes.

Moreover, the preparation may be in a solution form to which antibacterial activity is imparted to be usable as a multiple dosage form in divided dosing.

[2] Sustained Release or Immediate Release Preparation and its Production

A preferred sustained release preparation comprises a core comprising the compound of the present invention or a combination drug, which is optionally coated with a water-insoluble material or a swelling polymer. For example, a sustained release preparation for oral administration of a once-daily dosage form is preferred.

Examples of the water-insoluble material used for the coating agent include cellulose ethers such as ethyl cellulose, butyl cellulose, etc., cellulose esters such as cellulose acetate, cellulose propionate, etc., polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate, etc., acrylic acid polymers such as an acrylic acid/methacrylic acid copolymer, a methyl methacrylate copolymer, an ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymer, a polyacrylic acid, a polymethacrylic acid, a methacrylic acid alkylamide copolymer, a

poly(methyl methacrylate), a polymethacrylate, an aminoalkyl methacrylate copolymer, a poly(methacrylic anhydride), a glycidyl methacrylate copolymer, in particular, a series of Eudragits (Rohm & Pharma) such as Eudragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/chlorotrimethyl methacrylate/ethyl ammonium copolymer) and Eudragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), etc., hydrogenated oils such as hydrogenated castor oil (e.g., LUBRI WAX (Freund Industrial Co., Ltd.), etc.), waxes such as carnauba wax, a fatty acid glycerin ester, paraffin, etc., polyglycerin fatty acid esters, etc.

The swelling polymer is preferably a polymer having an acidic removable group and exhibiting pH-dependent swelling, and a polymer having an acidic removable group, which undergoes a less swelling at an acidic pH such as in the stomach but is swollen extensively at a neutral pH such as in the small and large intestines, is preferred.

Examples of such a polymer having an acidic removable group and exhibiting pH-dependent swelling include a crosslinked polyacrylic acid polymer such as Carbomers 934P, 940, 941, 974P, 980, 1342, etc., polycarbophil and calcium polycarbophil (all manufactured by BF Goodrich Chemicals), Hivis Wakos 103, 104, 105 and 304 (all manufactured by Wako Pure Chemical Industries, Ltd.), etc.

The coating agent used in the sustained release preparation may further contain a hydrophilic material.

Examples of the hydrophilic material include a polysaccharide which may have a sulfate group, such as pullulan, dextrin, alkali metal alginates, etc., a polysaccharide having a hydroxyalkyl group or a carboxyalkyl group such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, etc., methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, etc.

The amount of the water-insoluble material contained in the coating agent of the sustained release preparation is about 30 to about 90% (w/w), preferably about 35 to about 80% (w/w), more preferably about 40 to about 75% (w/w), and the swelling polymer content is about 3 to about 30% (w/w), preferably about 3 to about 15% (w/w). The coating agent may further contain a hydrophilic material, and the amount of the hydrophilic material contained in the coating agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), more preferably about 5 to about 35% (w/w). As used herein, the % (w/w) above is used to mean a % by weight based on the coating agent composition, which is the remainder of the coating agent solution after removing

any solvent (e.g., water, a lower alcohol such as methanol, ethanol, etc.).

The sustained release preparation is manufactured by preparing a core containing a drug as illustrated below, followed by coating the resulting core with a coating agent solution obtained by heat-melting a water-insoluble material or a swelling polymer or by dissolving or dispersing such a material in a solvent.

I. Preparation of Drug-Containing Core

The shape of a core containing a drug to be coated with a coating agent (hereinafter sometimes simply referred to as a core) is not specifically limited but preferably prepared into a particulate shape such as granules, fine granules, or the like.

When the core is granules or fine granules, they have a mean particle size of preferably about 150 to about 2,000 μm, more preferably about 500 to about 1,400 μm.

The core can be prepared in a conventional manner. For example, a drug is mixed with a suitable excipient, binder, disintegrating agent, lubricant, stabilizer, etc., and then subjected to wet extrusion granulation, fluidized bed granulation, or the like.

The drug content in the core is about 0.5 to about 95% (w/w), preferably about 5.0 to about 80% (w/w), more preferably about 30 to about 70% (w/w).

Examples of the excipient contained in the core include a saccharide such assaccharose, lactose, mannitol, glucose, etc., starch, crystalline cellulose, calcium phosphate, cornstarch, etc. Among them, crystalline cellulose and cornstarch are preferred.

Examples of the binder used include polyvinyl alcohol, hydroxypropyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum arabic, gelatin, starch, etc. Examples of the disintegrating agent include calcium carboxymethyl cellulose (ECG505), sodium croscarmellose (Ac-Di-Sol), crosslinked polyvinyl pyrrolidone (crospovidone), a low substituted hydroxypropyl cellulose (L-HPC), etc. Among them, hydroxypropyl cellulose, polyvinyl pyrrolidone and a low substituted hydroxypropyl cellulose are preferred. Examples of the lubricant and the anticoagulant include talc, magnesium stearate and its inorganic salts, and examples of the lubricant include polyethylene glycol, etc. Examples of the stabilizer include an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc.

In addition to the technique described above, the core can be prepared by using other techniques such as an tumbling granulation technique, a pan coating technique, a fluidized bed coating technique and a melt granulation technique, wherein a drug or a mixture of the drug with an excipient, a lubricant, etc. is portionwise added to inert

carrier particles as seeds for the core with spraying a binder dissolved in a suitable solvent such as water, a lower alcohol (e.g., methanol, ethanol, etc.) or the like. Examples of the inert carrier particles include those prepared fromsaccharose, lactose, starch, crystalline cellulose and waxes, and, preferably, these carriers have a mean particle size of about 100 μm to about 1,500 μm.

In order to separate the drug contained in the core from a coating agent, the surface of the core may be covered with a protective material. Examples of the protective material include the hydrophilic material described above and water-insoluble material. The preferred protective material is polyethylene glycol or a polysaccharide having a hydroxyalkyl group or a carboxyalkyl group, more preferably, hydroxypropylmethyl cellulose and hydroxypropyl cellulose. The protective material may contain, as a stabilizer, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc., and a lubricant such as talc. When the protective material is used, the amount thereof to be coated is about 1 to about 15% (w/w), preferably about 1 to about 10% (w/w), more preferably about 2 to about 8% (w/w) based on the core.

The protective material can be coated by a conventional coating method and specifically, the core is spray-coated with the protective material by a fluidized bed coating technique, a pan coating technique, etc.

II. Coating of Core with Coating Agent

The core obtained in I above is coated with a coating agent solution prepared by melt-heating the water-insoluble material and pH-dependent swelling polymer described above and a hydrophilic material or by dissolving or dispersing them in a solvent to obtain a sustained release preparation.

As a coating method of the core with the coating agent solution, there are, for example, spray-coating, etc.

The composition ratio of the water-insoluble material, swelling polymer and hydrophilic material in the coating agent solution can be appropriately chosen to be within the amounts of the respective components contained in the coating.

The amount of the coating agent is about 1 to about 90% (w/w), preferably about 5 to about 50% (w/w), more preferably about 5 to about 35% (w/w) based on the core (excluding the protective material coating).

As the solvent for the coating agent solution, water and an organic solvent can be used alone or as a mixture thereof. When a mixture is used, the ratio of water and the

organic solvent (water/organic solvent: a weight ratio) may vary with the range of 1 to 100%, and is preferably 1 to about 30%. The organic solvent is not particularly limited so far as it can dissolve the water-insoluble material, and examples of the solvent include a lower alcohol such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, etc., a lower alkanone such as acetone, acetonitrile, chloroform, methylene chloride, etc. Among them, a lower alcohol is preferred, with ethyl alcohol and isopropyl alcohol being more preferred. Water and a mixture of water and an organic solvent are used preferably as solvents for the coating agent solution. In this case, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid, etc. may be added to the coating agent solution, if necessary, for the purpose of stabilizing the coating agent solution.

To carry out the coating by spray coating, the coating can be made using a conventional coating method. Specifically, the core is sprayed with a coating agent solution by a fluidized bed coating technique, a pan coating technique, or the like. At this time, a lubricant such as talc, titanium oxide, magnesium stearate, calcium stearate, light silicic anhydride, etc., and a plasticizer such as glycerin fatty ester, hardened castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol, etc. may also be added.

After coating with a coating agent, an antistatic agent such as talc may also be admixed, if necessary.

The immediate release preparation may be a liquid (solution, suspension, emulsion, etc.) or a solid (particles, pills, tablets, etc.). An oral preparation and a parenteral preparation such as an injectable preparation may be used, and an oral preparation is preferred.

The immediate release preparation may usually contain a carrier, additives and an excipient (hereinafter sometimes abbreviated as excipients) which are conventionally used in the pharmaceutical field, in addition to a drug which is an active ingredient. The pharmaceutical excipients are not specifically limited so long as they are excipients conventionally used in the pharmaceutical field. Examples of the excipient for an oral solid preparation include lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, etc.), powdered sugar, granulated sugar, mannitol, light silicic anhydride, magnesium carbonate, calcium carbonate, L-cysteine, etc., with corn starch and mannitol being preferred. Any of these excipients may be employed alone or in combination with each other. The amounts of the excipients are, for example, about 4.5 to about 99.4 w/w %, preferably about 20 to

about 98.5 w/w %, more preferably about 30 to about 97 w/w %, based on the total weight of the immediate release preparation.

The content of drug in the immediate release preparation may appropriately be selected from about 0.5% through about 95%, preferably about 1% through about 60% to whole amount of the immediate release preparation.

When the immediate release preparation is an oral solid preparation, the preparation contains a disintegrating agent in addition to the components described above. Examples of the disintegrating agent include calcium carboxymethylcellulose (ECG505 manufactured by GOTOKU CHEMICAL Co., Ltd.), sodium croscarmellose (for example, Ac-Di-Sol manufactured by Asahi Kasei Corporation), crospovidone (for example, COLIDON CL manufactured by BASF), low-substituted hydroxypropyl cellulose (Shin-Etsu chemical Co., Ltd.), carboxymethyl starch (MATSUTANI CHEMICAL INDUSTRY Co., Ltd.), sodium carboxymethyl starch (EXORITAB manufactured by KIMURA SANGYO), partial α starch (PCS manufactured by Asahi Kasei Corporation), etc. For example, the disintegrating agent that disintegrates granules by water absorption or swelling upon contact with water, or forming a channel between the active component comprising the core and an excipient can be used. Any of these disintegrating agents can be used alone or in combination with each other. The amount of the disintegrating agent used may be appropriately chosen depending upon the type and the amount of the drug used or a particular preparation design for the intended release performance. For example, the amount is about 0.05 to about 30 w/w %, preferably about 0.5 to about 15 w/w % based on the total weight of the immediate release preparation.

When the immediate release preparation is an oral solid preparation, the preparation may optionally contain additives conventionally used in a solid preparation, in addition to the components described above. Examples of the additives include binders (for example, sucrose, gelatin, powdery gum arabic, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose, polyvinyl pyrrolidone, pullran, dextrin, etc.), lubricants (polyethylene glycol, magnesium stearate, talc, light silicic anhydride (for example, aerosil (NIPPON AEROSIL)), surfactants (for example, anionic surfactants such as sodium alkylsulfate, nonionic surfactants such as polyoxyethylene fatty ester, polyoxyethylene sorbitan fatty ester, polyoxyethylene castor oil derivatives, etc.), colorants (for example, tar colorants, caramel, colcothar, titanium oxide, riboflavins), if necessary, corrigents (for example,

sweeteners, flavors, etc.), adsorbents, preservatives, wetting agents, antistatic agents, etc. Furthermore, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid or the like can also be added as a stabilizer.

As the binder above, hydroxypropyl cellulose, polyethylene glycol and polyvinyl pyrrolidone, etc. are preferably used.

The immediate release preparation can be prepared by mixing the components described above and kneading the mixture, if necessary, and then molding according to a conventional technique for making pharmaceutical preparations. The mixing above can be carried out in a conventional manner, e.g., by mixing, kneading, etc. Specifically, where the immediate release preparation is in the form of particles, the preparation can be prepared by mixing components with a vertical granulator, a multi-purpose kneader (HATA IRON WORKS CO., LTD), a fluidized bed granulator FD-5S (POWREX CORPORATION) or thee like, and then granulating the resulting by wet extrusion granulation or fluidized bed granulation by a technique similar to that for preparing the core of the sustained release preparation described above.

The immediate release preparation and the sustained release preparation thus obtained can be compounded, as they are, or, together with appropriate pharmaceutical excipients, in pharmaceutical preparations separately in a conventional manner to prepare respective preparations for administering in combination with each other simultaneously or at certain time intervals. Alternatively, both preparations may be compounded in a single dosage form for oral administration (e.g., granules, fine granules, tablets, capsules) as they are, or, together with appropriate pharmaceutical excipients. Both preparations in the form of granules or fine granules may also be filled in a single capsule for oral administration.

[3] Sublingual, Buccal or Rapid Oral Disintegrating Preparation and its Production

A sublingual, buccal or rapid oral disintegrating preparation may be in the form of a solid preparation such as a tablet, or may be in the form of an oral mucosal patch (film).

The sublingual, buccal or rapid oral disintegrating preparation is preferably a preparation containing the compound of the present invention or a combination drug and an excipient. The preparation may also contain auxiliary agents such as a lubricant, an isotonizing agent, a hydrophilic carrier, a water-dispersible polymer, a stabilizer, etc. Further for the purpose of promoting the absorption and enhancing the bioavailability, the preparation may also contain β-cyclodextrin or β-cyclodextrin derivatives (e.g.,

hydroxypropyl-β-cyclodextrin, etc.).

Examples of the above excipient include lactose, saccharose, D-mannitol, starch, crystalline cellulose, light silicic anhydride, etc. Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc., with magnesium stearate and colloidal silica being preferred. Examples of the isotonizing agent include sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin and urea, with mannitol being particularly preferred. As the hydrophilic carrier, there are, for example, a swelling hydrophilic carrier such as crystalline cellulose, ethyl cellulose, crosslinked polyvinyl pyrrolidone, light silicic anhydride, silicic acid, dicalcium phosphate, calcium carbonate, etc., with crystalline cellulose (e.g., microcrystalline cellulose, etc.) being preferred. As the water-dispersible polymer, there are, for example, a gum (e.g., tragacanth gum, acacia gum, guar gum), alginate (e.g., sodium alginate), cellulose derivatives (e.g., methyl cellulose, carboxymethylcellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose), gelatin, water-soluble starch, polyacrylic acid (e.g., carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinyl pyrrolidone, polycarbophil, ascorbate palmitate salt, etc., with hydroxypropylmethyl cellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinyl pyrrolidone and polyethylene glycol being preferred. Hydroxypropylmethyl cellulose is particularly preferred. As the stabilizer, there are, for example, cysteine, thiosorbitol, tartatic acid, citric acid, sodium carbonate, ascrobic acid, glycine, sodium sulfite, etc., with citric acid and ascorbic acid being particularly preferred.

The sublingual, buccal or rapid oral disintegrating preparation can be prepared by mixing the compound of the present invention or a combination drug and an excipient by a method per se known. Furthermore, if desired, the auxiliary agents described above, such as the lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetener, preservative, etc. may also be admixed. After mixing the components described above simultaneously or at certain time intervals, the mixture is compressed into tablets to obtain the sublingual, buccal or oral quick disintegration tablet. In order to obtain a suitable hardness, a solvent such as water, an alcohol, etc. can be used to moisturize or wet the components before or after tabletting, followed by drying.

In preparing the oral mucosal patch (film), the compound of the present invention or a combination drug and the water-dispersible polymer (preferably,

hydroxypropyl cellulose, hydroxypropylmethyl cellulose), excipient, etc. described above are dissolved in a solvent such as water, etc. and then the resulting solution is cast into a film. In addition, additives such as a plasticizer, a stabilizer, an antioxidant, a preservative, a colorant, a buffering agent, a sweeteners, etc. may be added to the preparation. A glycol such as polyethylene glycol, propylene glycol, etc. may be added to impart an appropriate elasticity to a film, and a bioadhesive polymer (e.g., polycarbophile, carbopol) may also be added to enhance the adhesion of the film to the oral mucosal lining. The casting can be carried out by pouring a solution onto a non-adhesive surface, spreading the solution using a coater such as a doctor blade in a uniform thickness (preferably, approximately 10 to 1000 microns), and then drying the solution to form a film. The film thus formed is dried at room temperature or while warming, and then cut into pieces each having a desired surface area.

A preferred rapid oral disintegrating preparation is, for example, a rapid diffusion preparation in a solid network form, which comprises the compound of the present invention or a combination drug and a water-soluble or water-diffusible carrier inert to the compound of the present invention or the combination drug. The network is formed by sublimating a solvent from a solid composition comprising a solution of the compound of the present invention or a combination drug in a suitable solvent.

In addition to the compound of the present invention or a combination drug, the composition of the rapid oral disintegrating preparation may preferably contain a matrix-forming agent and a secondary component.

Examples of the matrix-forming agent include gelatins, dextrins and animal or vegetable proteins from soybean, wheat, psyllium seed, etc.; gummy materials such as gum arabic, guar gum, agar, xanthane gum, etc.; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinyl pyrrolidones; materials derived from gelatin-gum arabic complexes, etc. The matrix-forming agent further includes saccharides such as mannitol, dextrose, lactose, galactose, trehalose, etc.; cyclic saccharides such as cyclodextrins, etc.; inorganic salts such as sodium phosphate, sodium chloride, aluminum silicate, etc.; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine, etc.

One or more matrix-forming agents can be incorporated into a solution or suspension before solidification. The matrix-forming agents may be present in addition to a surfactant, or may be present in the absence of a surfactant. The matrix-forming

agents serve not only to form a matrix itself, but also assist to maintain diffusion of the compound of the present invention or a combination drug in the solution or suspension.

The composition may contain a secondary component such as a preservative, an antioxidant, a surfactant, a thickening agent, a colorant, pH adjusting agent, a flavor, a sweetener, a taste masking agent, etc. As the suitable colorant, there are, for example, iron oxide red, black and yellow, FD & C dyes available from ERIS & EVERALD such as FD & C Blue No. 2 and FD & C Red No. 40, etc. Examples of the suitable flavor include mint, raspberry, licorice, orange, lemon, grape fruit, caramel, vanilla, cherry, grape flavor and a combination thereof. Examples of the suitable pH adjusting agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetener include aspartame, acesulfame K and thaumatine. Examples of the suitable taste masking agent include sodium bicarbonate, ion exchange resins, cyclodextrin inclusion compounds, adsorbents and microencapsulated apomorphine.

The preparation generally contains the compound of the present invention or a combination drug in an amount of about 0.1 to about 50% by weight, preferably about 0.1 to about 30% by weight and, preferably, the preparation (the sublingual tablet, buccal, etc. described above) allows 90% or more of the compound of the present invention or a combination drug to be dissolved (in water) within a time period of about 1 to about 60 minutes, preferably about 1 minute to about 15 minutes, more preferably about 2 minutes to about 5 minutes, or is a rapid oral disintegrating preparation which disintegrates within about 1 to about 60 seconds, preferably about 1 to about 30 seconds, more preferably about 1 to about 10 seconds, after being placed in the oral cavity.

The amount of the above excipient is about 10 to about 99% by weight, preferably about 30 to about 90% by weight based on the total weight of the preparation. The amount of β-cyclodextrin or β-cyclodextrin derivative is about 0 to about 30% by weight based on the total weight of the preparation. The amount of the lubricant is about 0.01 to about 10% by weight, preferably about 1 to about 5% by weight based on the total weight of the preparation. The amount of the isotonizing agent is about 0.1 to about 90% by weight, preferably about 10 to about 70% by weight based on the total weight of the preparation. The amount of the hydrophilic carrier is about 0.1 to about 50% by weight, preferably about 10 to about 30% by weight based on the total weight of the preparation. The amount of the water-dispersible polymer is about 0.1 to

about 30% by weight, preferably about 10 to about 25% by weight based on the total weight of the preparation. The amount of the stabilizer is about 0.1 to about 10% by weight, preferably about 1 to about 5% by weight based on the total weight of the preparation. If necessary, the preparation described above may further contain additives such as a colorant, a sweetener, a preservative, etc.

A dose of the combined preparations of the present invention varies depending upon kind of the compound of the present invention, age, body weight, conditions, dosage form, route for administration, dosing period, etc.

A dose of the compound of the present invention may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in oral administration, the compound is generally administered to the patient with cancer (as 60 kg body weight) in a daily dose of about 0.1 to about 100 mg, preferably about 1.0 to about 50 mg and more preferably about 1.0 to about 20 mg. In parenteral administration, a single dose of the compound may vary depending upon subject to be administered, target organ, conditions, route of administration, etc., and in the form of an injectable dosage form, it is advantageous to administer the compound to the patient with cancer (as 60 kg body weight) generally in a daily dose of about 0.01 to about 30 mg, preferably about 0.1 to about 20 mg, and more preferably about 0.1 to about 10 mg. For other animal species, the corresponding dose as converted per 60 kg weight can be administered. Of course, the dose may vary depending on individual conditions as described above; in such a case, a dose less than the dose given above may be sufficient, or may be higher than the range above.

It is possible to set any range of a dose for the combination drug, so long as it causes no adverse side effects. A daily dose of the combination drug may vary depending on the severity of disease, subject's age, sex, body weight and susceptibility, the dosing period and intervals, the characteristics, formulation, type and active components of the pharmaceutical preparation, etc. and is not particularly limited. For example, in oral administration, the dose is about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, and more preferably about 0.1 to 100 mg in terms of a drug; usually, this dose is administered by dividing 1 to 4 times per day.

When the pharmaceutical preparations of the present invention are administered, the compound of the present invention and a combination drug may be administered at the same time. Alternatively, a combination drug is first administered and then the compound of the present invention is administered, or the compound of the

present invention is first administered and then a combination drug is administered. When they are administered at certain time intervals, the intervals vary depending on the active component to be administered, dosage form and route of administration; when a combination drug is first administered, the compound of the present invention may be administered within 1 minute to 3 days, preferably 10 minutes to 1 day, more preferably 15 minutes to 1 hour after the administration of the combination drug. When the compound of the present invention is first administered, a combination drug may be administered within 1 minute to 1 day, preferably 10 minutes to 6 hours, more preferably 15 minutes to 1 hour after the administration of the compound of the present invention.

As a preferred method of administration, for example, about 0.001 to 200 mg/kg of a combination drug in the form of an oral dosage preparation is administered orally and, after about 15 minutes, about 0.005 to 0.5 mg/kg of the compound of the present invention in the form of a parenteral preparation is administered parenterally as a daily dose.

As the metastins, there are used, for example, human metastin described in WO 00/24890, mouse or rat metastin described in WO 01/75104, etc.

Specific examples of human metastin include a peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, and the like.

The "peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues" may be any peptide, as far as it is a peptide containing the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, but means that these peptides have substantially the same physiological activity (e.g., a receptor binding activity, a signal transduction action, a sugar level elevating action, a pancreatic glucagon secretion promoting action, a urine formation promoting action, etc.). Specifically, there are used (i) a peptide having the amino acid sequence represented by SEQ ID NO: 1, (ii) a peptide having the N-terminal 47-54 amino acid sequence at the C terminus in the amino acid sequence represented by SEQ ID NO: 1 and consisting of 8 to 54 amino acid residues, etc.

More specifically, human metastin used includes (i) a peptide consisting of the amino acid sequence represented by SEQ ID NO: 1 (human metastin 54 (1-54)), (ii) a

peptide consisting of the N-terminal 40-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 15 (40-54); SEQ ID NO: 15), (iii) a peptide consisting of the N-terminal 45-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 10 (45-54); SEQ ID NO: 16), (iv) a peptide consisting of the N-terminal 46-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 9 (46-54); SEQ ID NO: 17), (v) a peptide consisting of the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by (human metastin 8 (47-54); SEQ ID NO: 18), etc.

As mouse metastin (A), there are used, for example, (i) a peptide containing the N-terminal 134-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3 and consisting of 8 to 52 amino acid residues. Specific examples of mouse metastin (A) used include (i) a peptide consisting of the N-terminal 90-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, (ii) a peptide consisting of the N-terminal 132-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, (iii) a peptide consisting of the N-terminal 127-141 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 3, and the like.

As mouse metastin (B), there are used, for example, (i) a peptide containing the N-terminal 138-145 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 5 and consisting of 8 to 52 amino acid residues. Specific examples of mouse metastin (B) used include (i) a peptide consisting of the N-terminal 94-145 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 5, and the like.

As rat metastin, there are used, for example, (i) a peptide containing the N-terminal 112-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7 and consisting of 8 to 52 amino acid residues. Specific examples of rat metastin used include (i) a peptide consisting of the N-terminal 68-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, (ii) a peptide consisting of the N-terminal 110-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, (iii) a peptide consisting of the N-terminal 105-119 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 7, and the like.

Throughout the specification, the metastins are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at

the left hand and the C-terminus (carboxyl terminus) at the right hand. In the peptide represented by SEQ ID NO: 1, the C-terminus may be in any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide ($-CONH_2$) and an ester (-COOR). Herein, examples of the ester group shown by R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl such as a phenyl-C_{1-2} alkyl group, e.g., benzyl, phenethyl, etc.; an α-naphthyl-C_{1-2} alkyl group such as α-naphthylmethyl, etc.; pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Furthermore, the metastins include peptides, wherein the amino group at the N-terminal methionine residue is protected with a protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.); those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent (e.g., -OH, -SH, amino group, imidazole group, indole group, guanidino group, etc.) on the side chain of an amino acid in the molecule is protected with a suitable protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.), or conjugated peptides such as glycopeptides bound to sugar chains.

For salts of the metastins of the present invention, preferred are salts with physiologically acceptable acids (e.g., inorganic acids or organic acids) or bases (e.g., alkali metal salts), etc., especially physiologically acceptable acid addition salts. Examples of such salts include salts with, for example, inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid); salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid) and the like.

As the DNAs encoding metastins, there are used, for example, DNAs encoding human metastin described in WO 00/24890, DNAs encoding mouse or rat metastin described in WO 01/75104, etc.

The DNAs encoding the metastins may be any of genomic DNA, genomic DNA library, cDNA derived from the cells and tissues described above, cDNA library derived from the cells and tissues described above and synthetic DNA. The vector to be used for the library may be any of bacteriophage, plasmid, cosmid and phagemid. The DNA may also be directly amplified by reverse transcriptase polymerase chain reaction

(hereinafter abbreviated as RT-PCR) using the total RNA or mRNA fraction prepared from the cells and tissues described above.

The DNA encoding human metastin, mouse metastin precursor (A), mouse metastin precursor (B) or rat metastin precursor may be any DNA, so long as each is a DNA containing a base sequence represented by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8, or a DNA having a base sequence hybridizable to the base sequence represented by any base sequence represented by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 under highly stringent conditions and encoding the human metastin, mouse metastin (A), mouse metastin (B) or rat metastin described above.

Specific examples of the DNA hybridizable to the base sequence represented by any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 under highly stringent conditions include DNAs containing a base sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology and the most preferably at least about 95% homology, to the base sequence represented by any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8.

Homology in the base sequence can be measured under the following conditions (an expectation value = 10; gaps are allowed; filtering = ON; match score = 1; mismatch score = -3) using the homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

The hybridization can be carried out by per se publicly known methods or by modifications of these methods, for example, according to the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989). A commercially available library may also be used according to the instructions of the attached manufacturer's protocol. Preferably, the hybridization can be carried out under highly stringent conditions.

The highly stringent conditions used herein are, for example, those in a sodium concentration at about 19 to 40 mM, preferably about 19 to 20 mM at a temperature of about 50 to 70°C, preferably about 60 to 65°C. In particular, hybridization conditions in a sodium concentration of about 19 mM at a temperature of about 65°C are most preferred.

Specifically, as the DNA encoding the human metastin consisting of the amino acid sequence represented by SEQ ID NO: 1, the DNA consisting of the base sequence

represented by SEQ ID NO: 2 is used. Accordingly, for the base sequence encoding the human metastin consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 1 may be chosen from the base sequence represented by SEQ ID NO: 2.

As the DNA encoding the mouse metastin precursor (A) comprising the amino acid sequence represented by SEQ ID NO: 3, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 4, and the like. Accordingly, for the base sequence encoding the mouse metastin precursor (A) consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 3 may be chosen from the base sequence represented by SEQ ID NO: 4.

As the DNA encoding the mouse metastin precursor (B) comprising the amino acid sequence represented by SEQ ID NO: 5, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 6, and the like. Accordingly, for the base sequence encoding the mouse metastin precursor (B) consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 5 may be chosen from the base sequence represented by SEQ ID NO: 6.

As the DNA encoding the rat metastin comprising the amino acid sequence represented by SEQ ID NO: 7, there are employed a DNA consisting of the base sequence represented by SEQ ID NO: 8, and the like. Accordingly, for the base sequence encoding the rat metastin consisting of the various amino acid sequences described above, a base sequence corresponding to each of the partial amino acid sequences in the amino acid sequence represented by SEQ ID NO: 7 may be chosen from the base sequence represented by SEQ ID NO: 8.

More specifically, for the peptide consisting of the amino acid sequence represented by SEQ ID NO: 1 (human metastin 54 (1-54)), a DNA containing the base sequence represented by SEQ ID NO: 2, etc. is used.

For the peptide consisting of the N-terminal 40-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 15 (40-54); SEQ ID NO: 15), a DNA containing the base sequence represented by SEQ ID NO: 19, etc. is used.

For the peptide consisting of the N-terminal 45-54 amino acid sequence in the

amino acid sequence represented by SEQ ID NO: 1 (human metastin 10 (45-54); represented by SEQ ID NO: 16), a DNA containing the base sequence represented by SEQ ID NO: 20, etc. is used.

For the peptide consisting of the N-terminal 46-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 9 (46-54); represented by SEQ ID NO: 17), a DNA containing the base sequence represented by SEQ ID NO: 21, etc. is used.

For the peptide consisting of the N-terminal 47-54 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1 (human metastin 8 (47-54); represented by SEQ ID NO: 18), a DNA containing the base sequence represented by SEQ ID NO: 22, etc. is used.

As the metastin receptor, its partial peptides or salts thereof, there are used, for example, a human metastin receptor, its partial peptides or salts thereof described in WO 00/24890, a mouse or rat human metastin receptor, its partial peptides or salts thereof described in WO 01/75104, etc.

Specifically, the metastin receptor includes a protein containing the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, etc.

The amino acid sequence which has substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 includes, for example, an amino acid sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology, and most preferably at least about 95% homology, to the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13.

Homology of the amino acid sequences can be determined under the following conditions (an expectation value = 10; gaps are allowed; matrix = BLOSUM62; filtering = OFF) using a homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

As the protein having substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, preferred is a protein having substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 and having the activity of the same nature as that of a protein consisting of the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, etc.

As the activity of substantially the same nature, there are, for example, a ligand binding activity, a signal transduction activity, and the like. The "substantially the same nature" is used to mean that the nature of these activities is equivalent in terms of quality. Thus, the activities such as a ligand binding activity, a signal transduction activity, etc. are preferably equivalent (e.g., about 0.01 to 100 times, preferably about 0.1 to 10 times, more preferably 0.5 to 2 times), but differences in degree such as a level of these activities, quantitative factors such as a molecular weight of the protein may be present and allowable.

The activities such as a ligand binding activity, a signal transduction activity, etc. can be assayed by per se publicly known method with modifications and may be determined according to methods of determining a ligand or screening methods described in, e.g., WO 00/24890 or WO 01/75104.

Examples of the metastin receptor used include proteins comprising (1) (i) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, of which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are deleted; (ii) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, to which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are added; (iii) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, in which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are inserted; (iv) the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, in which at least 1 or 2 (preferably about 1 to about 30, more preferably about 1 to about 10 and most preferably several (1 or 2)) amino acids are substituted by other amino acids; or (v) a combination of these amino acid sequences; and the like.

Throughout the specification, the metastin receptors are represented in accordance with the conventional way of describing peptides, that is, the N-terminus (amino terminus) at the left hand and the C-terminus (carboxyl terminus) at the right hand. In the metastin receptors including the metastin receptor represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13, the C-terminus may be in any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide (-$CONH_2$) and an ester (-COOR). Herein, examples of the ester group shown by R include a C_{1-6} alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, etc.; a C_{3-8} cycloalkyl group such as

cyclopentyl, cyclohexyl, etc.; a C_{6-12} aryl group such as phenyl, α-naphthyl, etc.; a C_{7-14} aralkyl such as a phenyl-C_{1-2} alkyl group, e.g., benzyl, phenethyl, etc.; an α-naphthyl-C_{1-2} alkyl group such as α-naphthylmethyl, etc.; and pivaloyloxymethyl group, which are widely used as an ester for oral use, and the like.

Where the metastin receptors contain a carboxyl group (or a carboxylate) at a position other than the C-terminus, the carboxyl group may be amidated or esterified and such amides or esters are also included within the receptor protein of the present invention. In this case, the ester group used may be the same group as the C-terminal esters described above.

Furthermore, the metastin receptors include those wherein the amino group at the N-terminal methionine residue is protected with a protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.); those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent (e.g., -OH, -SH, amino group, imidazole group, indole group, guanidino group, etc.) on the side chain of an amino acid in the molecule is protected with a suitable protecting group (e.g., a C_{1-6} acyl group such as a C_{2-6} alkanoyl group, e.g., formyl group, acetyl group, etc.), or conjugated proteins such as glycoproteins bound to sugar chains.

Specific examples of the metastin receptors include human metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 9, rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 11, mouse metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 13, etc.

The partial peptides of the metastin receptor (hereinafter sometimes simply referred to as the partial peptide) may be any peptide, so long as they are partial peptides of the metastin receptor described above; there are used those such as protein molecules of the metastin receptor, which are the sites exposed outside the cell membrane, and having a ligand binding activity.

Specifically, the partial peptide of the metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 13 is a peptide containing the parts analyzed to be extracellular domains (hydrophilic domains) in the hydrophobic plotting analysis. A peptide containing a hydrophobic domain in part can be used as well. In addition, the peptide may contain each domain separately or a plurality of domains together.

In the metastin receptor, preferred partial peptides are those having the number of amino acids of at least 20, preferably at least 50, and more preferably at least 100, in the amino acid sequence described above, which constitutes the metastin receptor.

The partial peptide may be a peptide having the amino acid sequence described above, of which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are deleted; to which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are added; or, in which at least 1 or 2 (preferably about 1 to about 10 and more preferably several (1 or 2)) amino acids are substituted by other amino acids.

In the partial peptide, the C terminus may be any form of a carboxyl group (-COOH), a carboxylate (-COO-), an amide (-CONH$_2$) and an ester (-COOR), as in the metastin receptor described above.

Furthermore, the partial peptides include peptides, wherein the amino group at the N-terminal methionine residue is protected with a protecting group; those wherein the N-terminal region is cleaved in vivo and the glutamyl group thus formed is pyroglutaminated; those wherein a substituent on the side chain of an amino acid in the molecule is protected with a suitable protecting group, or conjugated peptides such as glycopeptides bound to sugar chains, as in the metastin receptors described above.

For salts of the metastin receptor or the partial peptide, preferred are salts with physiologically acceptable acids, especially physiologically acceptable acid addition salts. Examples of the salts include salts with, for example, inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid); salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid) and the like.

As the DNA encoding the metastin receptor or its partial peptides, there are used, for example, a DNA encoding the human metastin receptor or its partial peptides described in WO 00/24890, a DNA encoding the mouse or rat human metastin receptor or its partial peptides described in WO 01/75104, etc.

The DNAs encoding the metastin receptor or its partial peptides may be any of genomic DNA, genomic DNA library, cDNA derived from the cells and tissues described above, cDNA library derived from the cells and tissues described above and synthetic DNA. The vector to be used for the library may be any of bacteriophage, plasmid, cosmid and phagemid. The DNA may also be directly amplified by reverse

transcriptase polymerase chain reaction (hereinafter abbreviated as RT-PCR) using the total RNA or mRNA fraction prepared from the cells and tissues described above.

Specifically, the DNA encoding human metastin receptor, mouse metastin receptor or rat metastin receptor may be any DNA, so long as it is a DNA containing each base sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14, or a DNA containing a base sequence hybridizable to the base sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14 under highly stringent conditions and encoding a receptor having the activity of substantially the same nature (e.g., a ligand binding activity, a signal transduction activity, etc.) as that of the human metastin receptor, mouse metastin receptor or rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14.

Examples of the DNA hybridizable to the base sequence represented by any of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14 include DNAs containing a base sequence having at least about 70% homology, preferably at least about 80% homology, more preferably at least about 90% homology and the most preferably at least about 95% homology, to the base sequence represented by any of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14.

Homology in the base sequence can be measured under the following conditions (an expectation value = 10; gaps are allowed; filtering = ON; match score = 1; mismatch score = -3) using the homology scoring algorithm NCBI BLAST (National Center for Biotechnology Information Basic Local Alignment Search Tool).

The hybridization can be carried out by per se publicly known methods or by modifications of these methods, for example, according to the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989), etc. A commercially available library may also be used according to the instructions of the attached manufacturer's protocol. Preferably, the hybridization can be carried out under highly stringent conditions.

The highly stringent conditions used herein are, for example, those in a sodium concentration at about 19 to 40 mM, preferably about 19 to 20 mM at a temperature of about 50 to 70°C, preferably about 60 to 65°C. In particular, hybridization conditions in a sodium concentration of about 19 mM at a temperature of about 65°C are most preferred.

More specifically, as the DNA encoding the human metastin receptor

consisting of the amino acid sequence represented by SEQ ID NO: 9, the DNA consisting of the base sequence represented by SEQ ID NO: 10 is used.

As the DNA encoding the rat metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 11, the DNA consisting of the base sequence represented by SEQ ID NO: 12 is used.

As the DNA encoding the mouse metastin receptor consisting of the amino acid sequence represented by SEQ ID NO: 13, the DNA consisting of the base sequence represented by SEQ ID NO: 14 is used.

The metastin receptors, their partial peptides or salts thereof and the DNAs encoding the metastin receptors or their partial peptides can be obtained or produced by the methods described in WO 00/24890 or WO 01/75104.

The present invention will be described in detail by referring to EXAMPLES, FORMULATION EXAMPLES AND TEST EXAMPLES, but is not deemed to be limited thereto, and any modification may be made without departing from the scope of the present invention.

In the following EXAMPLES, the term "room temperature" normally means a temperature of about 10°C to 35°C. In percentages, the yield is shown by mol/mol% and the solvent used in chromatography by vol%, and the remaining by wt%. In proton NMR spectra, data on OH, NH protons, etc. that are broad and unidentified are not shown.

The other abbreviations used in the specification mean as follows.

Abbreviation	Description
10Ψ,CSNH:	C-terminal-$CONH_2$ at the 10-position is substituted with -$CSNH_2$.
1Ψ2,CH_2NH:	The -CONH- bond between the 1- and 2-positions is substituted with the -CH_2NH- bond.
2Ψ3,CH_2NH:	The -CONH- bond between the 2- and 3-positions is substituted with the -CH_2NH- bond.
3Ψ4,CH_2NH:	The -CONH- bond between the 3- and 4-positions is substituted with the -CH_2NH- bond.
4Ψ5,CH_2NH:	The -CONH- bond between the 4- and 5-positions is substituted with the -CH_2NH- bond.
6Ψ7,CSNH:	The -CONH- bond between the 6- and 7-positions is substituted with the -CSNH- bond.
6Ψ7,NHCO:	The -CONH- bond between the 6- and 7-positions is substituted with

the -NHCO- bond.

6Ψ7,CH_2NH: The -CONH- bond between the 6- and 7-positions is substituted with the -CH_2NH- bond.

6Ψ7,CH_2O: The -CONH- bond between the 6- and 7-positions is substituted with the -CH_2O- bond.

7Ψ8,CH_2NH: The -CONH- bond between the 7- and 8-positions is substituted with the -CH_2NH- bond.

8Ψ9,CH_2NH: The -CONH- bond between the 8- and 9-positions is substituted with the -CH_2NH- bond.

9Ψ10,CH_2NH: The -CONH- bond between the 9- and 10-positions is substituted with the -CH_2NH- bond.

Abu : 2-aminobutanic acid

Ac : acetyl

Acp : 6-aminocaproic acid

AcOEt : ethyl acetate

AcOH : acetic acid

Aib : α-aminoisobutanoic acid

Ala(2-Qui) : 2-quinolylalanine

Ala(3-Bzt) : 3-benzothienylalanine

Alb : Albizziin 2-amino-3-ureidopropion acid

Arg(Ac): N^{ω}-acetylarginine

Arg(Boc_2,Me) : $N^{\omega,\omega'}$-bis-tert-butoxycarbonyl-N^{ω}-methylarginine

Arg(Et) : N^{ω}-ethylarginine

Arg(Me) : N^{ω}-methylarginine

Arg(asyMe_2) or Arg(Me_2)asym : asymmetric-$N^{\omega,\omega}$-dimethylarginine

Arg(symMe_2) or Arg(Me_2)sym : symmetric-$N^{\omega,\omega'}$-dimethylarginine

Arg(NO_2) : N^{ω}-methylarginine

Arg(n-Pr) : N^{ω}-propylarginine

Arg(Tos) : N^{ω}-tosylarginine

Asp(NHMe) : N^{ω}-methylasparagine

Asp(Nme2) : N^{ω}-dimethylasparagine

AzaGly : azaglycine

AzaPhe : azaphenylalanine

Aze(2) : azetidine-2-carboxylic acid

β-Ala	: β-alanine
Boc	: tert-butoxycarbonyl
Boc_2O	: di-tert-butyl dicarbonate
Br-Z	: 2-bromobenzyloxycarbonyl
Bu^t	: tert-butyl
Bzl	: benzyl
CDI	: 1,1'-carbonyldiimidazole
Cha	: cyclohexylalanine
CIP	: 2-chloro-1,3-dimethylimidazolium tetrafluoroborate
Cit	: citrulline
Clt resin	: 2-chlorotrytyl resin
Cl-Z	: 2-chlorobenzyloxycarbonyl
Dab	: 2,4-diaminobutanoic acid
Dap	: 2,3-diaminopropionic acid
Dap(Ac)	: N^{β}-acetyldiaminopropionic acid
Dap(For)	: N^{β}-formyldiaminopropionic acid
Dap(Gly)	: N^{β}-glycyldiaminopropionic acid
Dap(GnGly)	: N^{β}-(N-guanidinoglycyl)diaminopropionic acid
DCM	: dichloromethane
DEA	: diethylamine
DIEA	: N,N-diisopropylethylamine
DIPCDI	: 1,3-diisopropylcarbodiimide
DMAP	: 4-dimethylaminopyridine
DMF	: N,N-dimethylformamide
EDT	: 1,2-ethanedithiol
Fmoc	: 9-fluorenylmethoxycarbonyl
For	: formyl
γ-Abu	: 4-aminobutanoic acid
γ-MeLeu	: γ-methylleucine
Gn	: guanidino
GuAmb	: 4-guanidinomethylbenzoyl
Har	: homoarginine
Har(Me)	: N^{ω}-methylhomoarginine
HOAt	: 1-hydroxy-7-azabenzotriazole

HOBt	: 1-hydroxybenzotriazole
HONB	: N-hydroxy-5-norbornene-2,3-dicarboxamide
Hph	: homophenylalanine
Hyp	: trans-4-hydroxyproline
IndPr	: 3-(indol-3-yl)propionyl
$Lys(Me_2)$	: $N^{\varepsilon,\varepsilon}$-dimethyllysine
MBHA	: p-methylbenzhydrylamine
MeOH	: methanol
Mtt	: 4-methyltrytyl
$N((CH_2)_3Gn)Gly$	: N-(3-guanidinopropyl)glycine
Nal(1)	: 1-naphthylalanine
Nal(2)	: 2-naphthylalanine
Nar	: norarginine
Nar(Me)	: N^{ω}-methylnorarginine
Nle	: norleucine
NMeArg	: N^{α}-methylarginine
NMeAsn	: N^{α}-methylasparagine
NMeLeu	: N^{α}-methylleucine
NMePhe	: N^{α}-methylphenylalanine
NMeSer	: N^{α}-methylserine
NMeTrp	: N^{α}-methyltryptophan
NMeTyr	: N^{α}-methyltyrosine
Nva	: Norvaline
Orn	: ornithine
Orn(Mtt)	: N^{δ}-(4-methyltrytyl)ornithine
PAL	: 5-(4-(9-fluorenylmethoxycarbonyl)aminomethyl3,5-dimethoxy-phenoxy)valeric acid
Pbf	: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
pGlu	: pyroglutamic acid
Phe(2Cl)	: 2-chlorophenylalanine
Phe(2F)	: 2-fluorophenylalanine
$Phe(3,4Cl_2)$	: 3,4-dichlorophenylalanine
$Phe(3,4F_2)$	: 3,4-difluorophenylalanine
$Phe(3CF_3)$	: 3-trifluoromethylphenylalanine

Phe(3Cl) : 3-chlorophenylalanine
Phe(3F) : 3-fluorophenylalanine
Phe(4Cl) : 4-chlorophenylalanine
Phe(4CN) : 4-cyanophenylalanine
Phe(4F) : 4-fluorophenylalanine
Phe(4Gn) : 4-guanidinophenylalanine
Phe($4NH_2$) : 4-aminophenylalanine
Phe($4NO_2$) : 4-nitrophenylalanine
Phe(4CN) : 4-cyanophenylalanine
Phe(F_5) : pentafluorophenylalanine
PheΨ(CH_2O)Gly : The -CONH- bond between Phe and Gly is substituted with the -CH_2O- bond.
PheΨ(CSNH)-NH_2 : The C-terminal phenylalanylamide is substituted with the phenylalanylthioamide.
Phg : phenylglycine
PhOH : phenol
PhSMe : thioanisole
Pip(2) : 2-aminopipecolinic acid
Pro : proline
Pya(2) : 2-pyridylalanine
Pya(3) : 3-pyridylalanine
Pya(4) : 4-pyridylalanine
PyAOP : (7-azabenzotriazole-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP : (benzotriazole-1-yloxy)-tris(pyrrolidino)phosphonium hexafluorophosphate
PyBrop : bromo-tris(pyrrolidino)phosphonium hexafluorophosphate
Sar : N-methylglycine
Ser(Ac) : O-acetylserine
Ser(Me) : O-methylserine
Thi : 2-thienylalanine
Tic : 1,2,3,4-tetrahydroisoquinoline-2-caarboxylic acid
TIS : triisopropylsilane
Tle : tert-leucine

Tos : tosyl
Trp(For) : N^{in}-formyltryptophan
Trt : trytyl
Tyr(Me) : O-methyltyrosine
TyrΨ(CH_2NH)Asn : The -CONH- bond between Tyr and Asn is substituted with the -CH_2NH- bond.
TFA : trifluoroacetic acid
TFE : trifluoroethanol
Z : benzyloxycarbonyl

In the specification and drawings, the codes of bases and amino acids are denoted in accordance with the IUPAC-IUB Commission on Biochemical Nomenclature or by the common codes in the art, examples of which are shown below. For amino acids that may have the optical isomer, L form is presented unless otherwise indicated.

DNA : deoxyribonucleic acid
cDNA : complementary deoxyribonucleic acid
A : adenine
T : thymine
G : guanine
C : cytosine
Y : thymine or cytosine
N : thymine, cytosine, adenine or guanine
R : adenine or guanine
M : cytosine or adenine
W : thymine or adenine
S : cytosine or guanine
RNA : ribonucleic acid
mRNA : messenger ribonucleic acid
dATP : deoxyadenosine triphosphate
dTTP : deoxythymidine triphosphate
dGTP : deoxyguanosine triphosphate
dCTP : deoxycytidine triphosphate
ATP : adenosine triphosphate

EDTA	: ethylenediaminetetraacetic acid
SDS	: sodium dodecyl sulfate
TFA	: trifluoroacetic acid
EIA	: enzyme immunoassay
Gly or G	: glycine
Ala or A	: alanine
Val or V	: valine
Leu or L	: leucine
Ile or I	: isoleucine
Ser or S	: serine
Thr or T	: threonine
Cys or C	: cysteine
Met or M	: methionine
Glu or E	: glutamic acid
Asp or D	: aspartic acid
Lys or K	: lysine
Arg or R	: arginine
His or H	: histidine
Phe or F	: phenylalanine
Tyr or Y	: tyrosine
Trp or W	: tryptophan
Pro or P	: proline
Asn or N	: asparagine
Gln or Q	: glutamine
pGlu	: pyroglutamic acid

The sequence identification numbers in the sequence listing of the specification indicates the following sequence, respectively.

SEQ ID NO: 1

This shows the amino acid sequence of human-derived metastin (Metastin).

SEQ ID NO: 2

This shows the base sequence of DNA encoding human metastin.

SEQ ID NO: 3

This shows the amino acid sequence of mouse metastin precursor (A).

SEQ ID NO: 4

This shows the base sequence of DNA encoding mouse metastin precursor (A), which is the base sequence contained in plasmid pCMV-mKiSS-1 harbored on transformant Escherichia coli DH10B/pCMV-mKiSS-1.

SEQ ID NO: 5

This shows the amino acid sequence of mouse metastin precursor (B).

SEQ ID NO: 6

This shows the base sequence of DNA encoding mouse metastin precursor (B), which is the base sequence contained in plasmid pCR2.1-mKiSS-1.4A harbored on transformant Escherichia coli DH5α/pCR2.1-mKiSS-1.4A.

SEQ ID NO: 7

This shows the amino acid sequence of rat-derived metastin precursor.

SEQ ID NO: 8

This shows the base sequence of DNA encoding rat metastin precursor.

SEQ ID NO: 9

This shows the amino acid sequence of human OT7T175 (metastin receptor).

SEQ ID NO: 10

This shows the base sequence of DNA encoding human OT7T175 (metastin receptor).

SEQ ID NO: 11

This shows the amino acid sequence of rat OT7T175 (metastin receptor).

SEQ ID NO: 12

This shows the base sequence of DNA encoding rat OT7T175 (metastin receptor).

SEQ ID NO: 13

This shows the amino acid sequence of mouse OT7T175 (metastin receptor).

SEQ ID NO: 14

This shows the base sequence of DNA encoding mouse OT7T175 (metastin receptor).

SEQ ID NO: 15

This shows the amino acid sequence of human metastin 15 (40-54).

SEQ ID NO: 16

This shows the amino acid sequence of human metastin 10 (45-54) (MS10).

SEQ ID NO: 17

This shows the amino acid sequence of human metastin 9 (46-54).

SEQ ID NO: 18

This shows the amino acid sequence of human metastin 8 (47-54).

SEQ ID NO: 19

This shows the base sequence of DNA encoding human metastin 15 (40-54).

SEQ ID NO: 20

This shows the base sequence of DNA encoding human metastin 10 (45-54).

SEQ ID NO: 21

This shows the base sequence of DNA encoding human metastin 9 (46-54).

SEQ ID NO: 22

This shows the base sequence of DNA encoding human metastin 8 (47-54).

The transformant *Escherichia coli* DH10B/pCMV-mKiSS-1 has been on deposit since January 24, 2000 with International Patent Organisms Depository, National Institute of Advanced Industrial Science and Technology (the former Ministry of International Trade and Industry, Agency of Industrial Science and Technology, National Institute of Bioscience and Human Technology (NIBH)), located at Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (postal code 305-8566), Japan as the Accession Number FERM BP-7003 and since December 16, 1999 with Institute for Fermentation (IFO), located at 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japan, as the Accession Number IFO 16348.

The transformant *Escherichia coli* DH5α/pCR2.1-mKiSS-1.4A has been on deposit since March 6, 2000 with International Patent Organisms Depository, National Institute of Advanced Industrial Science and Technology (the former Ministry of International Trade and Industry, Agency of Industrial Science and Technology, National Institute of Bioscience and Human Technology (NIBH)), located at Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki (postal code 305-8566), Japan as the Accession Number FERM BP-7073 and since February 16, 2000 with Institute for Fermentation (IFO), located at 2-17-85 Juso-Honmachi, Yodogawa-ku, Osaka-shi, Osaka, Japan, as the Accession Number IFO 16360.

In the present invention, Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2 (SEQ ID NO: 16) is referred to as metastin 10 (Metastin10), i.e., MS10.

In EXAMPLES later described, the N-terminal Tyr and the C-terminal Phe in

MS10 are counted as the 1- and 10-positions, respectively.

Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2
1 2 3 4 5 6 7 8 9 10

For example, [Hph10]MS10 of Compound No. 79 (EXAMPLE 1) means a peptide wherein the C-terminal Phe (10-position) of MS10 is substituted with Hph.

For example, des(1)-MS10 of Compound No. 4 means a peptide wherein the N-terminal Tyr (1-position) is deleted.

For example, des(1-3)-Fmoc-MS10 of Compound No. 53 means a peptide wherein the N-terminal Tyr-Asn-Trp (1 to 3-positions) is deleted and the amino group of Asn at the 4-position is modified and protected with Fmoc.

[EXAMPLE 1]

(Synthesis Process A): Preparation of [Hph10]MS10 (Compound No. 79)

Using 51 mg of Fmoc-Hph-PAL resin (sub. 0.39 mmol/g), which was prepared by introducing Fmoc-Hph into commercially available PAL resin, the peptide chain was extended on a multiple peptide synthesizer ACT-396 to give Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Hph-PAL resin. To 18.2 mg of the resin, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was shaken for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution was performed with eluants A/B: 73/27-63/37 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.6 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.5 (Calcd. 1316.7)

Elution time on HPLC: 20.6 min

Elution conditions

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 2]

(Synthesis Process B): Preparation of [Trp(For)10]MS10 (Compound No. 186)

Using 379 mg of Fmoc-Arg(Pbf)-O-Clt resin (sub. 0.33 mmol/g), which was prepared by introducing Fmoc-Arg(Pbf)-OH into commercially available 2-chlorotritylchloride resin (Clt resin,1.33 mmol/g), the peptide chain was extended on ABI 433A to give 540 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)-O-Clt resin. To 270 mg of the peptide, 10 mL of AcOH/TFE/DCM (1/1/8) was added the mixture was shaken for 30 minutes. After the resin was removed by filtration, the solvent was concentrated and the residue was dissolved in AcOEt. The solution was then washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to the residue to give 68 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)-OH as the precipitate. To 22 mg of the peptide, 4 mg of HCl H-Trp(For)-NH_2 (prepared by treating Boc-Trp(For)-NH_2 with 9.7 N HCl/dioxane at 0°C for 30 minutes), 10 mg of PyAOP, 5 mg of HOAt and 11 μL of DIEA were added. The mixture was stirred for 15 hours. After the solvent was concentrated, chloroform-diethyl ether was added to the residue to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Pbf)Trp(For)-NH_2 as the precipitate. To the peptide, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours.. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 73/27-63/37 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1369.3 (Calcd. 1369.6)

Elution time on HPLC: 19.6 min

Elution conditions

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 3]

(Synthesis Process C): Preparation of [10Ψ,CSNH]MS10 (Compound No. 128)

After 264 mg of Boc-Phe-NH_2 was dissolved in 20 mL of THF, 1.62 g of Lawesson's reagent was added to the solution, followed by stirring for 24 hours. Insoluble matters were removed by filtration, the solvent was concentrated and the concentrate was dissolved in AcOEt. The solution washed over satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 275 mg (yield 98%) of (S)-2-tert-Butoxycarbonylamino-3-phenylpropanethioamide (Boc-PheΨ(CSNH)-NH_2) as the precipitate. After 42 mg of the peptide was treated at 0°C with 9.7 N HCl to remove Boc, the removal of Fmoc with 10% DEA/DMF treatment followed by condensation by the PyBOP/HOBt method were repeated to give 66 mg of Fmoc-LeuArg(Pbf)PheΨ(CSNH)-NH_2 (yield 93%). To 17mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGly-OH prepared as in EXAMPLE 2, H-LeuArg(Pbf)PheΨ(CSNH)-NH_2 (prepared by treating 14 mg of Fmoc-LeuArg(Pbf)PheΨ(CSNH)-NH_2 with 10% DEA/DMF), 9 mg of PyBrop, 3 mg of HOAt and 7 mL of DIEA were added and the mixture was stirred for 15 hours. After the solvent was concentrated, chloroform-diethyl ether was added thereto for precipitation. To 10 mg of the product, 100 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 72/28-62/38 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1318.4 (Calcd. 1318.6)

Elution time on HPLC: 21.8 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 4]

(Synthesis Process D): Preparation of [6Ψ7,CH_2NH]MS10 (Compound No. 163)

Using 321 mg of Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A to give Fmoc-LeuArg(Pbf)Phe-PAL resin. To a half volume of the peptide, Fmoc-Gly was condensed to give 190 mg of Fmoc-GlyLeuArg(Pbf)Phe-PAL resin. After 76 mg of the product was subjected to Fmoc deprotection, 2 mL of DMF, 50 μL of AcOH, 46 mg of Fmoc-Phe-H and 8 mg of $NaBH_3CN$ were added thereto, followed by shaking an hour. After the resin washed, 2 mL of DMF, 22 μL of DIEA and 18 μL of Z-Cl were added thereto and the mixture was shaken for 3 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(CH_2NZ)GlyLeuArg(Pbf)Phe-PAL resin. Under ice cooling, 46 μL of TMS-Br, 42 μL of PhSMe, 38 μL of m-cresol, 18 μL of EDT and 227 μL of TFA were added to 15 mg of the peptide an the mixture was stirred for 2 hours. After the solvent was removed by distillation, diethyl ether was added to the residue, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 72/28-62/38 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1288.7 (Calcd. 1288.7)

Elution time on HPLC: 18.2 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

(REFERENCE EXAMPLE 1)

Preparation of N-methyl-N,N'-Bis-Boc-1-guanylpyrazole

Under a nitrogen flow, 720 mg of 60% NaH in oil was dissolved in 20 mL of dry DMF and 20 mL of dry DMF solution of 5.59 g of N,N'-Bis-Boc-1-guanylpyrazole commercially available was added to the solution at 0°C, followed by stirring for 10 minutes. After 1.68 mL of methyl iodide was added thereto, the mixture was stirred at room temperature for 24 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography (ethyl acetate/n-hexane = 1/4) using silica gel 60 (200 mL) to give 5.35 g (yield 91.6%) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.69 (br s, 1H), 6.42 (dd, 1H, J=2.7, 1.5 Hz), 3.25 (s, 3H), 1.53 (s, 9H), 1.30 (s, 9H)

Elemental analysis as $C_{15}H_{24}N_4O_4$

Calcd.: C, 55.54; H, 7.46; N, 17.27

Found: C, 55.36; H, 7.48; N, 17.06

Rf1: 0.64, Rf2: 0.79

Developing solvent for TLC: Rf1 (ethyl acetate/n-hexane = 1/2), Rf2 (methanol/chloroform = 2/98)

Elution time on HPLC: 26.7 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-20/80, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (40 mins.)

Flow rate: 1.0 ml/min.

(REFERENCE EXAMPLE 2)

Preparation of N-methyl-N,N'-Bis-Z-1-guanylpyrazole

In an argon atmosphere, 40 mg of 60% NaH in oil was dissolved in 5 mL of

dry DMF and 5 mL of dry DMF solution of 380 mg of N,N'-Bis-Z-1-guanylpyrazole commercially available was added to the solution at 0°C, followed by stirring for 10 minutes. After 125 μL of methyl iodide was added thereto, the mixture was stirred at room temperature for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated to give 393 mg of the crude product. From the crude product 170 mg was purified by flush column chromatography (ethyl acetate/n-hexane = 1/4) using silica gel 60 (75 mL) to give 152 mg (yield 89.5%) of N-methyl-N,N'-bis-Z-1-guanylpyrazole.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (br s, 1H), 7.61 (d, 1H, J=1.0Hz), 7.37-7.32 (m, 4H), 7.29-7.26 (m, 4H), 7.16-7.13 (m, 2H), 6.36 (dd, 1H, J=2.8, 1.6 Hz), 5.18 (s, 2H), 5.04 (s, 2H), 3.22 (s, 3H)

Elemental analysis as $C_{21}H_{20}N_4O_4$

Calcd.: C, 64.28; H, 5.14; N, 14.28

Found: C, 64.09; H, 5.24; N, 14.43

Rf1: 0.50, Rf2: 0.86

Developing solvent for TLC: Rf1(ethyl acetate/n-hexane=1/2), Rf2(methanol/chloroform=2/98)

Elution time on HPLC: 28.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-20/80, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (40 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 5]

(Synthesis Process E): Preparation of [Arg(Me)9]MS10 (Compound No. 82)

Using 480 mg of Fmoc-Phe-Rink Amide MBHA resin, which was prepared by introducing Fmoc-Phe into Rink Amide MBHA resin commercially available, the peptide chain was extended on ABI 433A to give 1080 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuOrn(Mtt)Phe-Rink Amide MBHA resin. To 540 mg of the peptide, 10 mL of TFA/TIS/DCM (1/5/94) was added and the mixture was shaken for 50 minutes. The resin washed and then dried. After 2 mL of DMF, 49 mg of N-methyl-N,N'-bis-Boc-1-guanylpyrazole prepared in REFERENCE EXAMPLE 1 and 87 μL of DIEA were added to 2/5 volume of the resin,

the mixture was shaken for 15 hours to give 220 mg of Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuArg(Boc$_2$,Me)Phe-Rink Amide MBHA resin. To 50 mg of the peptide, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added and the mixture was stirred for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 10.5 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.5 (Calcd. 1316.7)

Elution time on HPLC: 20.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

N-Methyl-N,N'-bis-Boc-1-guanylpyrazole used to convert the amino acid at the 9-position into N^ω-methylated Arg in this EXAMPLE is a reagent useful for producing peptides containing N^ω-methylated Arg, and is advantageously used also in general peptides to produce peptides containing N^ω-methylated Arg characterized by reacting N-methyl-N,N'-bis-Boc-1-guanylpyrazole with Orn in peptides followed by deprotection.

Furthermore, blood stability is improved by converting Arg into N^ω-methylated Arg not only in the N^ω-methylated Arg-containing peptide obtained in this EXAMPLE but also in general peptides. Therefore, substituents on the side chain of N^ω-methylated Arg are useful for a method of enhancing blood stability, which comprises converting Arg in a peptide into N^ω-methylated Arg.

Moreover, a method of enhancing blood stability, which comprises introducing one or two (preferably one) alkyl group, preferably C_{1-4} alkyl group, more preferably methyl group into the side chain of Arg in the Arg-containing peptide, may be provided. Herein, the Arg-containing peptide includes, for example, a peptide having a partial

peptide characterized by the structure -Arg-XXX-, wherein XXX represents an amino acid having optionally substituted aromatic ring group into the side chain, preferably Phe, Trp, Tyr, etc.

The N^{ω}-methylated Arg-containing peptides can also be produced using not only N-methyl-N,N'-bis-Boc-1-guanylpyrazole but N-methyl-N,N'-bis-Z-1-guanylpyrazole prepared in REFERENCE EXAMPLE 2.

[EXAMPLE 6]

(Synthesis Process F): Preparation of [6Ψ7,CSNH]MS10 (Compound No. 166)

In 10 mL of DMF, 503 mg of HCl H-Gly-OBu^t was dissolved and 1162 mg of Fmoc-Phe, 608 mg of HOBt, 1874 mg of PyBOP and 784 μL of DIEA were added at 0°C, followed by stirring for 4 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to give 1.48 g (yield 99%) of Fmoc-PheGly-OBu^t as the precipitate. After 250 mg of the product was dissolved in 10 mL of toluene, 404 mg of Lawesson's reagent was added to the solution, followed by stirring at 80°C for 2 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to the eluate to give 207 mg (yield 80%) of Fmoc-PheΨ(CSNH)Gly-OBu^t as the precipitate. To 103 mg of the product, TFA/H_2O (95/5) was added and the mixture was stirred for an hour. After the solvent was concentrated, diethyl ether was added to give 82.4 mg (yield 90%) of Fmoc-PheΨ(CSNH)Gly-OH as the precipitate. Using Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A and 80 mg of Fmoc-LeuArg(Pbf)Phe-PAL resin thus extended was subjected to Fmoc deprotection. Then 35 mg of Fmoc-PheΨ(CSNH)Gly-OH, 47 mg of PyBrop, 14 mg of HOAt and 35 μL of DIEA were added to the resin, followed by shaking for 15 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(CSNH)GlyLeuArg(Pbf)Phe-PAL resin. To 15 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Diethyl ether was added to

the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 77/23-57/43 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.0 mg of white powders.

Mass spectrum $(M+H)^+$ 1318.7 (Calcd. 1318.6)

Elution time on HPLC: 20.8 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 7]

(Synthesis Process G): Preparation of [AzaGly7]MS10 (Compound No. 176)

Using 321 mg of Fmoc-Phe-PAL resin, which was prepared by introducing Fmoc-Phe into commercially available PAL resin, the peptide chain was extended on ABI 433A and 80 mg of Fmoc-LeuArg(Pbf)Phe-PAL resin thus extended was subjected to Fmoc deprotection. After 2 mL of THF and 16 mg of CDI were added, the mixture was shaken for 2 hours. Then 6 μL of hydrazine monohydrate was added to the mixture. The mixture was shaken for an hour and the resin was then washed. After 39 mg of Fmoc-Phe, 93 mg of PyBrop, 27 mg of HOAt and 105 μL of DIEA were added to the system, followed by shaking for 2 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Pbf)Phe-PAL resin. To 25 mg of the product, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by shaking for 2 hours. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC

using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 5.5 mg of white powders.

Mass spectrum $(M+H)^+$ 1303.3 (Calcd. 1303.6)

Elution time on HPLC: 18.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 8]

(Synthesis Process H): Preparation of [D-Tyr1,AzaGly7,Arg(Me)9]MS10 (Compound No. 232)

Fmoc-Phe,Fmoc-Orn(Mtt) was introduced into 4 g (0.55mmol/g) of Rink Amide MBHA resin commercially available to prepare Fmoc-Orn(Mtt)-Phe- Rink Amide MBHA resin, and 50 mL of TFA/TIS/DCM (1/5/94) was added to the resin, followed by shaking for 50 minutes. After the resin washed, 40 mL of DCM and 2.27 g of N-methyl-N,N'-bis-Boc-1-guanylpyrazole prepared in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 9. The mixture was shaken for 15 hours to give 4.74 g of Fmoc-Arg(Boc_2,Me)Phe-Rink Amide MBHA resin. Separately, 145 mg of Fmoc-$NHNH_2$ HCl was suspended in 10 mL of THF. Under ice cooling, 89 mg of CDI and 87 mL of DIEA were added to the suspension, followed by stirring at room temperature for an hour. Under ice cooling, a solution of 224 mg of H-Leu-OBu^t HCl in 5 mL of DMF 5 mL was added to the mixture. While reverting to room temperature, the mixture was stirred for 18 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 230 mg (yield 99%) of Fmoc-AzaGly-Leu-OBu^t. To 187 mg of the product, 10 mL of TFA/H_2O (9/1) was added, followed by stirring for an hour. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether was added to give 143 mg of Fmoc-AzaGly-Leu-OH as the precipitate (yield 87%). The resulting Fmoc-AzaGly-Leu-OH, Trt-Phe was introduced into Fmoc-Arg(Boc_2,Me)Phe-Rink

Amide MBHA resin. To the thus prepared Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)Phe-Rink Amide MBHA resin, 50 mL of TFA/TIS/DCM (1/5/94) was added and the mixture was shaken for 50 minutes. After the resin washed and neutralized, Fmoc-Ser(Bu^t) and then Fmoc-Asn(Trt) were introduced thereinto. Using 80.3mg of the resulting Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin, the peptide chain was extended to give 97.2 mg of H-$_D$-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin.

To the resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 76/24-66/34 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 11.7 mg of white powders.

Mass spectrum $(M+H)^+$ 1317.0 (Calcd. 1317.6)

Elution time on HPLC: 21.0 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 9]

(Synthesis Process I): Preparation of des(1-3)-3-(3-pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10 (Compound No. 322)

After 48.2 mg of Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 8 was subjected to Fmoc deprotection, the resin was treated with 15.2 mg of 3-(3-pyridyl)propionic acid commercially available, 15.9μL of DIPCDI and 200 μL of 0.5M HOAt/DMF at room temperature for 90 minutes. After the resin obtained washed and dried, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT

(80/5/5/5/2.5/2.5) was added to the resin, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 80/20-60/40 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 6.0 mg of white powders.

Mass spectrum $(M+H)^+$ 987.4 (Calcd. 987.5)

Elution time on HPLC: 8.1 min

Elution conditions:

ColumnYMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 10]

(Synthesis Process J): Preparation of des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10 (Compound No. 273)

After Fmoc-Trp(Boc) was introduced into 48.2 mg of Fmoc-Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 8, the resin was subjected to Fmoc deprotection to give H-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin. The resin obtained was treated in DMF with 29.3 mg of N,N'-bis-Boc-1-guanylpyrazole and 34.8 μL of DIEA for 14 hours to give Amidino-Trp(Boc)Asn(Trt)Ser(Bu^t)Phe-AzaGly-LeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin. After the resin obtained washed and dried, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 78/22-58/42 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A

column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 0.6 mg of white powders.

Mass spectrum $(M+H)^+$ 1082.3 (Calcd. 1082.6)

Elution time on HPLC: 11.4 min

Elution conditions:

Column: YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 11]

(Synthesis Process K): Preparation of [6Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10 (Compound No. 319)

In 30 mL of MeCN, 5.99 g of Z-Phe was dissolved and 3.94 g of HONB and 4.59 g of WSCD HCl were added to the solution at 0°C, followed by stirring at room temperature for 4 hours. While keeping at 0°C, 3.4 mL of 25% NH_3 aq. solution and 10 mL of DMF were added to the mixture, followed by stirring for 4 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether was added to give 1.48 g (yield 99%) of Z-Phe-NH_2 as the precipitate. After 1.94 g of [Bis(trifluoroacetoxy)iodo]benzene was dissolved in 20 mL of MeCN and 5 mL of H_2O, 890 mg of Z-Phe-NH_2 prepared above and 972 μL of pyridine were added to the precipitate at 0°C, followed by stirring at room temperature for 15 hours. After the solvent was concentrated, the concentrate was subjected to liquid-liquid separation with diethyl ether-1N HCl aq. solution and the 1N HCl aq. solution layer was concentrated and then dried. Its half volume was dissolved in 5 mL of DMF, and 486 μL of mono-tert-butyl malonate and 540 mg of HOBt were added to the solution. Then, 2.08 g of PyBOP and 1394 μL of DIEA were added at 0°C to the mixture, followed by stirring at room temperature for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 304 mg (yield 33%) of Z-PheΨ(NHCO)Gly-OBu^t as the precipitate. After 154 mg of the product was dissolved

in 20mL of MeOH, 10% Pd-C was added to the solution, followed by catalytic hydrogenation for 2 hours in a hydrogen flow. After removal of the catalyst by filtration, the solvent was concentrated and dried. The residue was dissolved in 10 mL of MeCN 10 mL and 152 mg of Fmoc-OSu and 78 μL of DIEA were added to the solution, followed by stirring for 15 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and diethyl ether-petroleum ether was added to give 127 mg (yield 68%) of Fmoc-PheΨ(NHCO)Gly-OBu^t as the precipitate. Fmoc-Leu was introduced into 63 mg of Fmoc-Arg(Boc_2,Me)Phe-Rink Amide MBHA resin prepared in EXAMPLE 10. After Fmoc deprotection, Fmoc-PheΨ(NHCO)Gly-OH (prepared by treating 25 mg of Fmoc-PheΨ(NHCO)Gly-OBu^t with TFA for 3 minutes), 300 μL of 0.5M HOAt, 78 mg of PyAOP and 52 μL of DIEA were added to the resin, followed by shaking for 6 hours. After the resin washed, 2 mL of DMF, 9 μL of DIEA and 12 μL of Ac_2O were added to the resin, followed by shaking for 30 minutes. After the resin washed, the peptide chain was extended on ABI 433A to give Boc-D-Tyr(Bu^t)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheΨ(NHCO)GlyLeuArg(Boc_2,Me)Phe-Rink Amide MBHA resin. To 34 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (30 minutes) was performed with eluants A/B: 76/24-66/34 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 0.7 mg of white powders.

Mass spectrum $(M+H)^+$ 1316.3 (Calcd. 1316.7)

Elution time on HPLC: 18.7 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 12]

(Synthesis Process L): Preparation of [N((CH_2)$_3$Gn)Gly9]-MS10 (Compound No. 218)

Using 192 mg of Fmoc-Phe-Rink Amide MBHA resin, the peptide chain was extended on ABI 433A to give Fmoc-GlyPhe-Rink Amide MBHA resin. After a 1/4 volume of the product was subjected to Fmoc deprotection, 2 mL of DMF, 50 μL of AcOH, 5 mg of Boc-β-Ala-H and 16 mg of $NaBH_3CN$ were added thereto and the mixture was shaken for 30 minutes. After the resin washed, 71 mg of Fmoc-Leu, 56 mg of CIP, 27 mg of HOAt and 105 mL of DIEA were added, followed by shaking for 15 hours. After the resin washed, the peptide chain was extended on ABI 433A to give Z-Tyr(Bzl)Asn(Trt)Trp(Boc)Asn(Trt)Ser(Bu^t)PheGlyLeuN((CH_2)$_3$NHBoc)GlyPhe-Rink Amide MBHA resin. To the product, 1 mL of TFA/PhOH/H_2O/TIS/EDT (87.5/5/2.5/2.5/2.5) was added and the mixture was stirred for 2 hours. After the resin was removed by filtration and then concentrated, ether was added to the concentrate. A half volume of the resulting precipitate was dissolved in 500 μL of DMF, 9 mg of 1H-pyrazole-1-carboxamidine hydrochloride and 22 mL of DIEA were added to the solution, followed by stirring for 15 hours. The solvent was distilled off and ether was added to precipitate. Under ice cooling, 60 μL of PhSMe, 56 μL of m-cresol, 26 μL of EDT, 337 μL of TFA and 65 μL of TMSBr were added to the mixture, followed by stirring for 2 hours. After the solvent was distilled off, ether was added to the residue, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 74/26-64/36 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.8 mg of white powders.

Mass spectrum $(M+H)^+$ 1302.5 (Calcd. 1302.7)

Elution time on HPLC: 18.6 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (35 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 13]

(Synthesis Process M): Preparation of MS10 (Compound No. 3)

Commercially available p-methyl BHA resin (0.77 mmole/g resin) was charged in a reaction tank of peptide synthesizer ABI 430A. Thereafter, Boc-Phe.Boc-Arg(Tos), Boc-Leu.Boc-Gly, Boc-Phe.Boc-Ser(Bzl), Boc-Asn.Boc-Trp(For) and Boc-Asn.Boc-Tyr(Br-Z) were introduced into the resin in this order according to the Boc-strategy (DCC-HOBt) peptide synthesis to give the desired protected peptide resin. The resin, 0.11 g, was stirred at 0°C for 60 minutes in 10 ml of anhydrous hydrogen fluoride containing 1 ml of p-cresol and 1.2 ml of 1,4-butanediol. Thereafter the hydrogen fluoride was distilled off in vacuum. Diethyl ether was added to the residue and the precipitate was filtrated. To the precipitate 50% acetic acid aqueous solution was added for extraction and insoluble matters were removed. After the extract was sufficiently concentrated, the concentrate was applied to Sephadex (trade name) G-25 column (2.0 x 80 cm) filled with 50% acetic acid aqueous solution followed by development with the same solvent. The main fractions were collected and lyophilized to give 40 mg of white powders. A half volume of the powders was applied to column chromatography (2.6 x 60 cm) packed with LiChroprep (trade name) RP-18 followed by washing with 200 ml of water containing 0.1% TFA. Then linear density gradient elution was performed with 300 ml of 0.1% TFA in water and 300 ml of 0.1% TFA-containing 33% acetonitrile. The main fractions were collected and lyophilized to give 2.2 mg of the desired peptide.

Mass spectrum (M+H) 1302.5 (Calcd. 1302.6)

Elution time on HPLC: 18.7 min

Elution conditions:

Column: Wakosil-II 5C18T 4.6 x 100 mm

Eluant: linear density gradient elution with eluants A/B = 95/5-45/55, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 14]

(Synthesis Process N): Preparation of des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10 (Compound No. 279)

Fmoc-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc_2)Phe-Rink-Amide MBHA resin prepared in EXAMPLE 8 was subjected to Fmoc deprotection. To 64 mg (20 μmol) of H-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc_2)Phe-Rink Amide MBHA

resin, 1.5 mL of THF and 13 mg of CDI were added, followed by shaking for 2 hours. After 32 mg of tryptamine hydrochloride, 28 μL of DIEA and 500 μL of DMF were added to the mixture, followed by shaking for 24 hours. Thereafter the resin washed to give 2-(Indol-3-yl)ethylcarbamoyl-Asn(Trt)Ser(Bu^t)PheAzaGlyLeuArg(Me,Boc$_2$)Phe-Rink Amied MBHA resin. To 15 mg of the product, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 69/31-59/41 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 1.1 mg of white powders.

Mass spectrum $(M+H)^+$ 1040.2 (Calcd. 1040.5)

Elution time on HPLC: 20.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 15]

Preparation of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin

Commercially available Rink Amide MBHA resin, 5 g (0.4 mmol/g), was swollen in DMF, and treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Trp(Boc) was introduced by treating the resin at room temperature with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution for 90 minutes to give Fmoc-Trp(Boc)-Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. After the resin obtained washed and swollen with DCM, 50 mL of TFA/TIS/DCM (1/5/94) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated

until yellow coloration caused by free Mtt group in a TFA/TIS/DCM (1/5/94) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give 6.195 g of Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The resin was divided in half and the Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (1 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (1 mmol).

Separately, 1.745 g (6 mmol) of Fmoc-$NHNH_2$ HCl was suspended in 20 mL of DMF-THF (4:1). Under ice cooling, 973 mg (6 mmol) of CDI and 2.09 mL (12 mmol) of DIEA were added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 3.314 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

[EXAMPLE 16]

(Synthesis Process O): Preparation of des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 385)

After 100 mg (0.03 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 2 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Phe was introduced by treating the resin with 77.5 g (0.2 mmol) of Fmoc-Phe-OH, 31.8 μL (0.2 mmol) of DIPCDI and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. In a similar manner, Ser(^{t}Bu) and Asn(Trt) were introduced to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The obtained resin was subjected to Fmoc deprotection and treated with 77.6 mg (0.2 mmol) of Fmoc-$_D$-Pya(4)-OH, 104.2 mg (0.2 mmol) of PyAOP, 400 μL

(0.2 mmol) of 0.5M HOAt/DMF and 174.2 μL (0.2 mmol) of DIEA at room temperature for 90 minutes to introduce $_D$-Pya(4) and then $_D$-Tyr(^{t}Bu), followed by Fmoc deprotection. Thus, 135 mg of H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was obtained.

To the resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, followed by stirring for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 15 ml/min with eluants A/B: 79/21-69/31 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 100 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 6.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1204.5 (Calcd. 1204.6)

Elution time on HPLC: 8.2 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 17]

(Synthesis Process P): Preparation of des(1-6)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 393)

After 35.2 mg (0.015 mmol) of Fmoc-AzaGly-Leu-Arg(Boc$_2$,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 2 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. Separately, 19.2 μL (0.1 mmol) of dibenzylamine was dissolved in THF. Under ice cooling, 16.2 mg (0.1 mmol) of CDI and 2.6 μL (0.015

mmol) of DIEA were added to the solution, followed by stirring at room temperature for an hour. After Fmoc deprotection, the resulting solution was added to H-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, followed by stirring at room temperature for 15 hours.

To Bzl_2NCO-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained, 1 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added, and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min. with eluants A/B: 63/37-53/47 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 100 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 2.2 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 768.7 (Calcd. 768.4)

Elution time on HPLC: 16.9 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 18]

(Synthesis Process Q): Preparation of des(1-5)-Benzoyl-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10 (Compound No. 421)

After 1.80 g of Z-Phe was dissolved in 20 mL of MeOH,下 73 mg of DMAP and 1.38 g of WSCD HCl were added to the solution at 0°C, followed by stirring at 4°C for 12 hours. The solvent was concentrated and the concentrate was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated to

give Z-Phe-OMe as oil. After dissolving in 20 mL of dry THF, 196 mg of $LiBH_4$ was added to the solution, followed by stirring at room temperature for 15 hours. The solvent was concentrated and the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and ether-petroleum ether was added to the concentrate to give 1.45 g (yield 85%) of Z-Phe-ol as the precipitate. After 60 mg of 60% NaH was suspended in 10 mL of dry THF, 285 mg of Z-Phe-ol, 264 mg of 18-crown-6 and 1.48 mL of tert-butyl bromoacetate were added to the solution at 0°C. While reverting to room temperature, the mixture was stirred for 15 hours. After the solvent was distilled off in vacuum, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 217 mg (yield 54%) of Z-PheΨ(CH_2O)Gly-OBu^t as oil. After 160 mg of Z-PheΨ(CH_2O)Gly-OBu^t was dissolved in 20 mL of MeOH, 10% Pd-C was added to the solution, followed by catalytic hydrogenation for 3 hours in a nitrogen flow. The catalyst was removed by filtration and the solvent was concentrated followed by drying. The concentrate was dissolved in 15 mL of DCM, and 114 mg of Fmoc-Cl and 139 μL of DIEA were added to the solution, followed by stirring for 12 hours. After the solvent was distilled off, the residue was dissolved in AcOEt and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography. Diethyl ether-petroleum ether was added to give 150 mg (yield 77%) of Fmoc-PheΨ(CH_2O)Gly-OBu^t as the precipitate. To the precipitate, were added 31 mg (15 μmol) of H-LeuArg(Me,Boc_2)Trp(Boc)-Rink amide MBHA resin obtained in a manner similar to the process of EXAMPLE 15, 19 mg of Fmoc-PheΨ(CH_2O)Gly-OH (prepared by treating Fmoc-PheΨ(CH_2O)Gly-OBu^t with 50% TFA/DCM for an hour), 180 μL of 0.5M HOAt, 42 mg of PyBrop and 47 μL of DIEA. The mixture was shaken for 18 hours. After the resin washed, 5 mL of 20% piperidine/DMF was added to the resin, followed by stirring at room temperature for 30 minutes. After the resin washed, 9 μL of benzoyl chloride, 13 μL of DIEA and 1 mL of DMF 1 were added to the resin, followed by stirring at room temperature for 2 hours. After the resin washed and dried, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added to the resin, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting

precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 75/25-65/35 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 2.5 mg of white powders.

Mass spectrum $(M+H)^+$ 782.2 (Calcd. 782.4)

Elution time on HPLC: 22.1 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 19]

(Synthesis Process R): Preparation of des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10 (Compound No. 434)

After 1.54 mL of mono-tert-butyl malonate, 1.08 g of fluorenylmethanol and 61 mg of DMAP were dissolved in 20 mL of DCM 20, 1.15 g of WSCD HCl was added to the solution, followed by stirring at room temperature for 24 hours. The solvent was distilled off in vacuum, the residue was dissolved in AcOEt. The solution was then washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and the concentrate was purified by flush column chromatography to give 1.62 g (yield 96%) of tert-butyl fluorenylmethyl malonate. In 20 mL of TFA, 61 mg of tert-butyl fluorenylmethyl malonate was dissolved and the solution was stirred at room temperature for 2 hours. After the solvent was distilled off in vacuum, the residue was dissolved in AcOEt, followed by washing with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and purified by flush column chromatography to give 850 mg (yield 67%) of mono-fluorenylmethyl malonate. After 5 mL of 20% piperidine/DMF was added to 46 mg (15 μmol) of Fmoc-LeuArg(Me,Boc_2)Trp(Boc)-Rink amide MBHA resin prepared in a manner similar to EXAMPLE 15, the solution was shaken at room temperature for 30 minutes. After the resin washed, 42 mg of

mono-fluorenylmethyl malonate, 70 mg of PyBrop, 300 μL of 0.5M HOAt/DMF, 52 μL of DIEA and 1 mL of DMF were added to the resin, and the mixture was shaken for 15 hours. After this procedure was repeated twice, 8 μL of Ac_2O, 5 μL of DIEA and 2 mL of DCM were added, followed by stirring at room temperature for 30 minutes. After the resin washed and then dried, 5 mL of 20% piperidine/DMF was added to a half of the resin, followed by stirring at room temperature for 30 minutes. After the resin washed, 13 mg of dibenzylhydrazine, 28 mg of PyBrop, 120 μL of 0.5M HOAt/DMF, 21 μL of DIEA and 1 mL of DMF were added to the resin, followed by shaking for 15 hours. After the resin washed and then dried, 200 μL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added to the resin, followed by stirring for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (120 minutes) was performed with eluants A/B: 83/17-63/37 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 21.6 mg of white powders.

Mass spectrum $(M+H)^+$ 767.6 (Calcd. 767.4)

Elution time on HPLC: 14.5 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 20]

(Synthesis Process S): Preparation of des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 436)

After 340.1 mg (0.1 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated in 20 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated with 155.0 mg (0.4 mmol) of Fmoc-Phe-OH, 63.6 μL (0.4 mmol) of DIPCDI and 0.8 mL (0.4 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to introduce

Phe. After Fmoc-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was subjected to Fmoc deprotection and then treated with 49.2 mg (0.4 mmol) of 4-Pyridinecarboxylic acid, 63.6 µL (0.4 mmol) of DIPCDI and 0.8 mL (0.4 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. Then, the resin washed and dried to give 353.5 mg of 4-Pyridinecarbonyl-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. To the resulting resin, 3.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 15 ml/min with eluants A/B: 79/21-69/31 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 6 mL of water and 200 µL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 21.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 797.8 (Calcd. 797.4)

Elution time on HPLC: 8.8 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 21]

(Synthesis Process T): Preparation of des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 499)

After 170.1 mg (0.05 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 5 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated with 77.5

mg (0.2 mmol) of Fmoc-Phe-OH, 31.8 μL (0.2 mmol) of DIPCDI, and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to introduce Phe. In a similar manner, Ser(^{t}Bu) and Asn(Trt) were introduced to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was subjected to Fmoc deprotection and then treated with 30.0 mg (0.2 mmol) of phenylpropionic acid, 31.8 μL (0.2 mmol) of DIPCDI and 0.4 mL (0.2 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. Then, the resin washed and dried to give 209.6 mg of 3-Phenylpropionyl-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. To the resin obtained, 1.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min with eluants A/B: 71/29-61/39 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized. The white powders obtained were dissolved in 10 mL of water and 125 μL of ion exchange resin BioRAD AG1 x 8 AcO^- form was added to the solution. While manually stirring the solution sometimes, the reaction solution was settled for an hour. The solution was filtered through a membrane filter to remove the resin and give 5.2 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1025.3 (Calcd. 1025.5)

Elution time on HPLC: 13.6 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 22]

(Synthesis Process U): Preparation of des(1-5)-Benzoyl-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 431)

After 500 mg (2.56 mmol) of benzylhidrazine.2HCl was dissolved in DCM, the solution was cooled to -78°C on dry ice. Then, 727.1 mg (3.33 mmol) of Boc_2O and 0.982 ml (5.64 mmol) of DIEA were added to the solution. Dry ice was removed and the mixture was stirred for 30 minutes. After confirming by TLC that the reaction proceeded, 327 µl (2.82 mmol) of benzoyl chloride and 580.4 µl (3.33 mmol) of DIEA were added to the mixture, followed by stirring at room temperature overnight. Citric acid crystals were added to the reaction solution and the mixture was concentrated. A 10% citric acid aqueous solution was added to the mixture. The precipitated residue was extracted with AcOEt and the extract washed with 10% citric acid aqueous solution, 5% $NaHCO_3$ aq. solution and then satd. NaCl aq. solution, followed by drying over anhydrous Na_2SO_4. The residue obtained was crystallized from ether-hexane (1:1) to give 435.5 mg of white crystals.

After 46.3 mg (0.015 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-NH-Rink Amide MBHA resin was swollen in DMF, the resin was treated with 5 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed with DMF and treated in THF with 3.65 mg (0.023 mmol) of CDI at room temperature for an hour. Separately, 32.6 mg (0.1 mmol) of the white powders above were treated with 0.3 ml of 4N HCl/dioxane for an hour. The solvent was then distilled off and the residue washed with ether. The residue obtained was dissolved in THF, and 17.4 µl (0.1 mmol) of DIEA was added to the solution. The resulting solution was added to the resin, followed by stirring overnight. The resin washed and dried to give 29.5 mg of Benzoyl-AzaPhe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-NH-Rink Amide MBHA resin. To the resin obtained, 0.5 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed at a flow rate of 8 ml/min with eluants A/B: 66/34-56/44 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC SH-343-5 S-5, 120A column (20 x 250 mm). The fractions containing the product were collected and lyophilized to give 3.2 mg of white powders.

Mass spectrum $(M+H)^+$ 797.7 (Calcd. 797.4)

Elution time on HPLC: 15.3 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 23]

(Synthesis Process V): Preparation of des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10 (Compound No. 548)

Fmoc-Leu-OH was introduced into commercially available 2-chlorotritylchloride resin. After Fmoc deprotection, 5 mL of THF and 162 mg of CDI were added to 403 mg of Fmoc-Leu-O-Clt resin (sub. 0.62 mmol/g) obtained. The mixture was shaken for an hour. After 97 μL of hydrazine monohydrate was added to the system, the mixture was shaken for 2 hours and the resin was then washed. To the resin, 581 mg of Fmoc-Phe, 699 mg of PyBrop, 3 mL of 0.5M HOAt/DMF solution and 784 μL of DIEA were added, followed by shaking for 12 hours. After the resin washed, the peptide chain was extended on ABI 433A to give 0.47 g of Boc-$_D$-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-O-Clt resin. To the resin, 10 mL of AcOH/TFE/DCM (1/1/8) was added, followed by shaking for 30 minutes. The resin was removed by filtration and the solvent was concentrated. The residue was dissolved in chloroform and the resulting solution washed with satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated and AcOEt-diethyl ether was added to the concentrate to give 320 mg (yield 98%) of Boc-$_D$-Tyr(Bu^t)$_D$-Pya(4)Asn(Trt)Ser(Bu^t)PheAzaGlyLeu-OH as the precipitate. On the other hand, 5 mL of 4N HCl/AcOEt was added to 264 mg (1 mmol) of Boc-Phe-NH_2 under ice cooling, followed by stirring for 30minutes. The solvent was distilled off and ether was then added for precipitation. The precipitate was dissolved in 20 mL of DMF, and 455 mg of Fmoc-Orn(Boc), 540 mg of HOBt, 382 mg of WSCD.HCl and 348 μL of DIEA were added to the solution, followed by stirring for 6 hours. After the solvent was distilled off in vacuum, the residue was dissolved in ethyl acetate and the solution washed with 1N HCl aq. solution, satd. $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated. Ether-petroleum ether

was added to the concentrate to give 594.4 mg (yield 99%) of Fmoc-Orn(Boc)-Phe-NH_2 as the precipitate. Under ice cooling, 5 mL of 4N HCl/AcOEt was added to 132 mg of the product, followed by stirring for 30 minutes. After the solvent was distilled off, ether was added to give 111.1 mg (yield 94%) of Fmoc-Orn-Phe-NH_2.HCl as the precipitate. The precipitate was dissolved in 3 mL of chloroform/TFE (3/1), and 194 mg of N-methyl-N,N'-Bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 and 105 μL of DIEA were added to the solution, followed by stirring for 24 hours. After the solvent was distilled off, ether-petroleum ether was added to give 108.5 mg (yield 72%) of Fmoc-Arg(Boc_2,Me)-Phe-NH_2 as the precipitate. In 5 mL of THF, 38 mg of the product was dissolved and 142 mg of Lawesson's Reagent was added to the solution, followed by stirring for 15 hours. After the solvent was distilled off in vacuum, the residue was dissolved in ethyl acetate and the solution washed with $NaHCO_3$ aq. solution and then satd. NaCl aq. solution. After drying over Na_2SO_4, the solvent was concentrated. After purification by flush column chromatography, ether-petroleum ether was added to give 18.7 mg (yield 48%) of Fmoc-Arg(Me,Boc_2)-PheΨ(CSNH)-NH_2 as the precipitate. To 11 mg of the product, 1 mL of 10% DEA/DMF was added and the mixture was stirred for 2 hours. After the solvent was distilled off, the residue was dissolved in 1 mL of DMF, and 18 mg of Boc-D-Tyr(Bu^t)-D-Pya(4)-Asn(Trt)-Ser(Bu^t)-Phe-AzaGly-Leu-OH previously obtained, 7.6 mg of HOBt, 5.4 mg of WSCD.HCl and 4.9 μL of DIEA were added to the solution, followed by stirring for 15 hours. The solvent was distilled off and ether was added to the residue for precipitation. To the precipitate, 1 mL of TFA/PhSMe/m-cresol/TIS/EDT (85/5/5/2.5/2.5) was added, and the mixture was stirred for 2 hours. Ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated for washing. The residue was extracted with an aqueous acetic acid solution and the extract was filtered to remove the resin. Then, linear density gradient elution (60 minutes) was performed with eluants A/B: 82/18-72/28 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC D-ODS-5-ST S-5 120A column (20 x 150 mm). The fractions containing the product were collected and lyophilized to give 0.9 mg of white powders.

Mass spectrum $(M+H)^+$ 1181.5 (Calcd. 1181.6)

Elution time on HPLC: 14.9 min

Elution conditions:

Column: Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-0/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 24]

(Synthesis Process W): Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 550)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by

stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 6.394 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

After 3.197 g (1 mmol) of the resin obtained was swollen in DMF, the resin was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained washed with DMF, the resin was treated with 1.806 g (4 mmol) of Trt-Phe-OH.0.5AcOEt, 2.086 g (4 mmol) of PyAOP, 8 mL (4 mmol) of 0.5M HOAt/DMF and 2.787 mL (16 mmol) of DIEA at room temperature for 90 minutes to give Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin Phe. The resin obtained washed with DCM, after swelling, 30 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM (1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. The H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was neutralized with 5%-DIEA/DMF solution and washed with DMF. Thereafter, the resin was treated with 1.590 g (4 mmol) of Fmoc-Thr(^{t}Bu)-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M HOAt/DMF at room temperature for 90 minutes to introduce Thr(^{t}Bu). Subsequently, the Fmoc deprotection by treatment with 30 ml of 20% piperidine/DMF solution for 20 minutes and condensation by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu) were repeated so that Asn(Trt), $_D$-Trp(Boc), and $_D$-Tyr(^{t}Bu) were introduced to give Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained washed to give H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 188.7 μL (2 mmol) of Ac_2O and 348.4 μL (2 mmol) of DIEAin 20 mL of DMF at room temperature for 30 minutes to acetylate the N terminus. The resin was then washed and dried to give 4.168 g of Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc

)-Rink Amide MBHA resin.

To a half of the resin obtained, i.e., 2.111 g, 15 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5 /5/2.5 /2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the supernatant was removed. This procedure was repeated twice for washing. After the residue was extracted with an aqueous acetic acid solution, the extract was filtered to remove the resin and lyophilized to give crude peptide powders. With respect to the remaining half of the resin, deprotection was performed under the same conditions to give about 650 mg of crude peptide powders in total. About 50 mg each of the crude peptide obtained was purified by applying sequentially to linear density gradient elution (60 minutes) at a flow rate of 15 ml/min with eluants A/B: 71/29-61/39 using: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile on preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm). The fractions containing the product were collected and lyophilized to give 255.5 mg of white powders as the purified sample.

All of the white powders were dissolved in 200 mL of aqueous acetonitrile solution and 492 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 225.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1298.7 (Calcd. 1298.6)

Elution time on HPLC: 15.6 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 25]

: Preparation of Ac-des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 562)

After 5.455 g (0.455 mmol/g) of commercially available Rink Amide MBHA

resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 6.319 g (12 mmol) of Fmoc-Trp(Boc)-OH, 1.908 mL (12 mmol) of DIPCDI and 24 mL (12 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 3 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 75 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 40 mL of DCM-TFE (4:1) and 2.919 g (9 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 3.489 g (12 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 30 mL of DMF. Under ice cooling, a suspension of 1.849 mg (11.4 mmol) of CDI in 20 mL of THF and then 4.181 mL (24 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 8.2496 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

After 2.646 g (1 mmol) of the resin obtained was swollen in DMF, the resin was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, the resin was treated with 1.630 g (4 mmol) of Trt-Phe-OH, 2.086 g (4 mmol) of PyAOP, 8 mL (4 mmol) of 0.5M

HOAt/DMF and 2.787 mL (16 mmol) of DIEA at room temperature for 90 minutes to give Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin Phe. The resin obtained was washed with DCM, after swelling, 30 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM (1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. The H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained was neutralized with 5%-DIEA/DMF solution and washed with DMF. Thereafter, the resin was treated with 1.590 g (4 mmol) of Fmoc-Thr(^{t}Bu)-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M HOAt/DMF at room temperature for 90 minutes to introduce Thr(^{t}Bu). Subsequently, the Fmoc deprotection by treatment with 30 ml of 20% piperidine/DMF solution for 20 minutes and condensation by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu) were performed to give Fmoc-Asn(Trt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was Fmoc-deprotected. Then the resin was treated with 1.476 g (3.8 mmol) of Fmoc-$_D$-Pya(4)-OH, 2.086 mg (4 mmol) of PyAOP, 8 mL of 0.5 M HOAt/DMF (4 mmol) and 2.439 mL of DIEA (14 mmol) at room temperature for 90 minutes to introduce $_D$-Pya(4). Susequently, by the DIPCDI/HOAt method similar to introduction of Thr(^{t}Bu), $_D$-Tyr(^{t}Bu) was introduced to the resin to give Fmoc-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 30 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. The resin obtained was washed to give H-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was treated with 188.7 μL (2 mmol) of Ac_2O and 348.4 μL (2 mmol) of DIEA in 20 mL of DMF at room temperature for 30 minutes to acetylate the N terminus. The resin was then washed and dried to give 1 mmol of Ac-$_D$-Tyr(^{t}Bu)-$_D$-Pya(4)-Asn(Trt)-Thr(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

To the resin obtained, 30 mL of TFA/PhSMe/m-cresol/H_2O/TIS/EDT (80/5/5 /5/2.5 /2.5) was added and the mixture was stirred for 90 minutes. Diethyl ether was added to the reaction solution, the resulting precipitate was centrifuged and the

supernatant was removed. This procedure was repeated twice for washing. After the residue was extracted with an aqueous acetic acid solution, the extract was filtered to remove the resin and lyophilized to give 949.0 mg of crude peptide powders. About 50 mg each of the crude peptide obtained was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with initial eluants A/B: 90/10 for 8 minutes, A/B: 75/25, wherein it took 7 minutes to increase the concentration, and linear density gradient elution (60 minutes) with eluants A/B: 75/25-65/35 using eluant A: 0.05% TFA in water and eluant B: 0.05% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 361.1 mg of white powders as the purified sample.

All of the white powders obtained were dissolved in 200 mL of aqueous acetonitrile solution and 1.434 mL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 309.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1260.4 (Calcd. 1260.4)

Elution time on HPLC: 15.5 min

Elution conditions:

Column Wakosil-II 5C18 HG (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 26]

: Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10 (Compound No. 571)

After 2.5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Phe was introduced by treating the resin with 1.550 g (4 mmol) of Fmoc-Phe-OH, 0.636 mL (4 mmol) of DIPCDI and 8 mL (4 mmol) of 0.5M

HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Phe- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 1 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 25 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Phe-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 0.973 g (3 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin (1 mmol) to give H-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin (1 mmol).

Separately, 1.163 g (4 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 10 mL of DMF. Under ice cooling, a suspension of 0.568 mg (3.5 mmol) of CDI in 10 mL of THF and then 1.307 mL (7.5 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 3.134 g of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin.

Using this resin, 1.94 g of Trt-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin obtained by the condensation of Trt-Phe-OH 0.5AcOEt in similar to EXAMPLE 24, was washed with DCM. After swelling, 12 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until brownish yellow coloration caused by free Trt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Trt group was removed. By washing the resin, 1.66 g of H-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Phe-Rink Amide MBHA resin were obtained. Using 553 mg of the resin obtained, peptide chain was extended with the

peptide synthesizer ABI-433A (Fmoc/DCC/HOBt) to give H-D-Tyr(But)-D-Trp(Boc)-Asn(Trt)-Thr(But)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin. To this product, 5 mL of DMF, 111 mg of AcONB and 44 ml of DIEA was added and the resin was shaken for two hours. The resin was dried after washing to give 0.78 g of Ac-D-Tyr(But)-D-Trp(Boc)-Asn(Trt)-Thr(But)-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin. To the resin, 6 mL of TFA/thioanisole/m-cresol/H2O/TIS/EDT (80/5/5/5/2.5/2.5) was added and the resin was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 71/29-61/39 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give white powders as the purified sample. The purified sample was lyophilized. The crude peptide obtained in the similar manner using 553 mg of H-Phe-AzaGly-Leu-Arg(Boc2,Me)-Phe-Rink amide MBHA resin was purified on preparative HPLC to give total 237.6 mg of purified sample as white powders.

The white powders obtained, 236.1 mg were dissolved in 200 mL of aqueous acetonitrile solution and 935 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 204.6 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1259.5 (Calcd. 1259.6)

Elution time on HPLC: 13.2 min

Elution conditions:

Column YMC-AM301 (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 80/20-30/70, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25

mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 27]

: Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 579)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 1.297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed

by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 2 mmol of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

Using 868 mg (0.257 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, Thr(^{t}Bu), Alb, $_D$-Trp(Boc), and $_D$-Tyr(^{t}Bu) were introduced by repeating condensation using DCC/HOBt method with ABI 433A to give a H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Alb-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. N-terminus od the obtained resin was acetylated by treating with 111 mg (0.5 mmol) of AcONB and 87 μL (0.5 mmol) of DIEA in 5 mL of DMF at room temperature for 10 hours. Subsequently, the resin was washed and dried to give a Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Alb-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rin k Amide MBHA resin.

To the resin obtained, 6 mL of TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2.5 /2.5) was added, and the suspension was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 69/31-59/41 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 106.5 mg of white powders as the purified sample.

All the white powders obtained were dissolved in 100 mL of aqueous acetonitrile solution and 400 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour. The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 97.5 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1299.5 (Calcd. 1299.6)

Elution time on HPLC: 19.0 min

Elution conditions:

Column Wakosil-II (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

[EXAMPLE 28]

(Synthesis Process X): Preparation of Ac-des(1)-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10 (Compound No. 585)

After 5 g (0.4 mmol/g) of commercially available Rink Amide MBHA resin was swollen in DMF, the resin was treated with 50 ml of 20% piperidine/DMF solution for 20 minutes to remove the Fmoc group. After the resin obtained was washed with DMF, Trp(Boc) was introduced by treating the resin with 4.213 g (8 mmol) of Fmoc-Trp(Boc)-OH, 1.272 mL (8 mmol) of DIPCDI and 16 mL (8 mmol) of 0.5M HOAt/DMF solution at room temperature for 90 minutes to give Fmoc-Trp(Boc)- Rink Amide MBHA resin. In a similar manner, Orn(Mtt) was introduced to give 2 mmol of Fmoc-Orn(Mtt)-Trp(Boc)-Rink Amide MBHA resin. The resin obtained was washed with DCM, after swelling, 50 mL of TFA/TIS/TFE/DCM (1/5/19/75) was added, the mixture was shaken for 10 minutes and the solution was distilled off. This procedure was repeated until yellow coloration caused by free Mtt group in a TFA/TIS/TFE/DCM(1/5/19/75) solution disappeared when the solution was added, thus the Mtt group was removed.

The resulting Fmoc-Orn-Trp(Boc)-Rink Amide MBHA resin was neutralized with 5%-DIEA/DCM solution. After washing with DCM, 25 mL of DCM-TFE (4:1) and 1.946 g (6 mmol) of N-methyl-N,N'-bis-Boc-1-guanylpyrazole obtained in REFERENCE EXAMPLE 1 were added to the resin. DIEA was added to the mixture to adjust pH of the solution to 10, and the mixture was shaken for 15 hours to give Fmoc-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. Fmoc-Leu was introduced into the obtained resin as in the same manner described above. The Fmoc group was removed from the thus obtained Fmoc-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol) to give H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin (2 mmol).

Separately, 2.326 g (8 mmol) of Fmoc-$NHNH_2$.HCl was suspended in 20 mL of DMF. Under ice cooling, a suspension of 1.297 mg (8 mmol) of CDI in 20 mL of THF and then 2.787 mL (16 mmol) of DIEA was added to the suspension, followed by stirring at room temperature for an hour. The resulting reaction solution was added to H-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin described above, followed by stirring at room temperature for 15 hours. After completion of the reaction, the resin washed and dried to give 2 mmol of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

Using 868 mg (0.257 mmol) of Fmoc-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin, Thr(^{t}Bu), Dap(Mtt), $_D$-Trp(Boc) and $_D$-Tyr(^{t}Bu) were introduced by repeating condensation using DCC/HOBt method with ABI 433A to give a H-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Dap(Mtt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin. N-terminus od the obtained resin was acetylated by treating with 111 mg (0.5 mmol) of AcONB and 87 μL (0.5 mmol) of DIEA in 5 mL of DMF at room temperature for 4 hours. Subsequently, the resin was washed and dried to give a Ac-$_D$-Tyr(^{t}Bu)-$_D$-Trp(Boc)-Dap(Mtt)-Ser(^{t}Bu)-Phe-AzaGly-Leu-Arg(Boc_2,Me)-Trp(Boc)-Rink Amide MBHA resin.

To the resin obtained, 6 mL of TFA/ PhSMe/ m-cresol/ H_2O/ TIS/ EDT(80/ 5/ 5 /5/2.5 /2.5) was added, and the suspension was shaken for two hours. After removal of the resin by filtration, solvent was distilled off. By adding diethylether, precipitation was obtained. After centrifugation, washing by removal of the supernatant was repeated twice, and the residues were extracted with acetate solution. After the resin was removed by filtration, the fraction was purified by applying to preparative HPLC using YMC Pack R&D-ODS-5-B S-5, 120A column (30 x 250 mm) at a flow rate of 15 ml/min sequencially with linear density gradient elution (60 minutes) with eluants A/B: 71/29-61/39 using eluant A: 0.1% TFA in water and eluant B: 0.1% TFA-containing acetonitrile. The fractions containing the product were collected and lyophilized to give 106.5 mg of white powders as the purified sample.

All the white powders obtained were dissolved in 100 mL of aqueous acetonitrile solution and 400 μL of ion exchange resin AG1 x 8 AcO^- form, which was obtained by converting commercially available BioRAD AG1 x 8 Cl^- form into the acetate type in a conventional manner, was added to the solution. While manually stirring the reaction solution sometimes, the reaction solution was settled for an hour.

The solution was concentrated to remove acetonitrile as much as possible. The concentrate was then filtered through a membrane filter and lyophilized to give 58.3 mg of white powders as the acetate.

Mass spectrum $(M+H)^+$ 1284.7 (Calcd. 1284.6)

Elution time on HPLC: 17.9 min

Elution conditions:

Column Wakosil-II (4.6 x 100 mm)

Eluant: linear density gradient elution with eluants A/B = 100/0-50/50, using 0.1% TFA in water as eluant A and acetonitrile containing 0.1% TFA as eluant B (25 mins.)

Flow rate: 1.0 ml/min.

The structures of compounds synthesized as in EXAMPLES 1 to 24 and physicochemical properties of these compounds are shown in TABLES 1 to 11, below.

[TABLE 1]

Comp. No.		M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode	Synth Proc
1	Metastin	5858.4	5858.5	18.1	d	M
2	Lys-Asp-Leu-Pro-Asn-MS10	1869.6	1869.9	18.6	d	M
3	MS10	1302.5	1302.6	15.7	d	M
4	des(1)-MS10	1139.6	1139.6	18.1	d	M
17	[Pya(4)10]MS10	1303.6	1303.6	14.7	d	M
18	[Tyr(Me)10]MS10	1332.7	1332.7	17.7	d	M
19	[Phe(2F)10]MS10	1320.5	1320.6	17.8	d	M
23	[Tyr5]MS10	1378.6	1378.8	18.6	d	M
24	[Leu5]MS10	1328.7	1328.7	19.8	d	M
30	Acetyl-MS10	1344.5	1344.6	29.2	b	A
31	Fmoc-MS10	1524.6	1524.7	23.1	b	A
38	[D-Ser5]MS10	1302.5	1302.6	11.8	c	A
39	[D-Asn4]MS10	1302.5	1302.6	11.6	c	A
40	[D-Trp3]MS10	1302.5	1302.6	11.5	c	A
41	[D-Asn2]MS10	1302.5	1302.6	11.7	c	A
42	[D-Tyr1]MS10	1302.5	1302.6	11.4	c	A
44	[Lys9]MS10	1274.6	1274.6	11.7	c	A
45	[Ala8]MS10	1260.5	1260.6	10.0	c	A
50	[Ala7]MS10	1316.3	1316.7	12.2	c	A
51	[NMePhe10]MS10	1316.3	1316.7	22.7	a	A
53	des(1-3)-Fmoc-MS10	1061.2	1061.5	27.3	a	A
54	des(1-2)-Fmoc-MS10	1247.4	1247.6	29.6	a	A
55	des(1)-Fmoc-MS10	1361.6	1361.6	28.2	a	A
56	[Lys2]MS10	1316.6	1316.7	16.8	d	M
57	[Asp2]MS10	1303.7	1303.6	17.7	d	M
58	[Tyr2]MS10	1351.7	1351.7	18.2	d	M
59	[Leu2]MS10	1301.6	1301.7	19.2	d	M
60	[Pya(3)10]MS10	1303.6	1303.6	14.7	d	M
61	[Phe(4F)10]MS10	1320.6	1320.6	18.0	d	M
67	[Ala3]MS10	1187.4	1187.6	9.3	c	A
68	[Leu3]MS10	1229.6	1229.6	11.1	c	A
69	[Ser3]MS10	1203.5	1203.6	8.9	c	A
70	[Asp3]MS10	1231.6	1231.6	9.0	c	A
71	[Lys3]MS10	1244.6	1244.7	8.1	c	A
72	[Ala1]MS10	1210.5	1210.6	11.1	c	A
73	[Leu1]MS10	1252.6	1252.7	12.5	c	A
74	[Ser1]MS10	1226.6	1226.6	10.9	c	A
75	[Asp1]MS10	1254.4	1254.6	11.0	c	A

[TABLE 2]

76	[Lys1]MS10	1267.6	1267.7	10	c	A
77	[Phe(4CN)10]MS10	1327.5	1327.6	17.2	d	M
78	[Trp(For)3, Phe(4CN)10]MS10	1355.6	1355.6	17.4	d	M
79	[Hph10]MS10	1316.5	1316.7	20.6	a	A
81	[NMeArg9]MS10	1316.3	1316.7	23.3	a	A
82	[Arg(Me)9]MS10	1316.5	1316.7	20.1	a	E
83	[Arg(Me2)asy9]MS10	1330.4	1330.7	21.3	a	A
87	des(4-5)-Boc-MS10	1201.6	1201.6	22.5	d	M
88	des(4-5)-MS10	1101.5	1101.5	18.6	d	M
90	[Lys9,9Ψ10,CH2NH]MS10	1260.6	1260.7	19.8	a	D
91	[8Ψ9,CH2NH]MS10	1288.7	1288.7	20.5	a	D
97	[Har9]MS10	1316.3	1316.7	11.9	c	A
98	[Lys(Me2)9]MS10	1302.6	1302.7	11.8	c	A
101	[Ser7]MS10	1332.6	1332.6	11.6	c	A
105	[Nle8]MS10	1302.3	1302.6	11.9	c	A
107	[Val8]MS10	1288.5	1288.6	11	c	A
109	[Tyr10]MS10	1408.4	1408.7	10.2	c	A
110	[Nal(2)10]MS10	1332.4	1332.6	13.5	c	A
111	[Phe(F5)10]MS10	1392.2	1392.6	13.5	c	A
112	[Cha10]MS10	1308.4	1308.7	13.4	c	A
114	des(1-3)-3-(3-Indolyl)propionyl-MS10	1010.5	1010.5	13.8	c	A+I
121	des(1-4)-[Trp5]MS10	824.3	824.5	22.5	d	M
123	[NMeLeu8]MS10	1316.7	1316.7	12.7	c	A
126	[NMeSer5]MS10	1317	1316.7	11.8	c	A
127	[D-Asn4,NMePhe6]MS10	1316.7	1316.7	11.8	c	A
128	[10Ψ,CSNH]MS10	1318.4	1318.6	21.8	a	C
129	[Arg(Me2)sy9]MS10	1331.2	1330.7	20.9	a	A
130	[Phe(4Cl)10]MS10	1336.4	1336.6	13.1	c	A
131	[Phe(4NH2)10]MS10	1317.4	1317.6	8.3	c	A
132	[Phe(4NO2)10]MS10	1347.4	1347.6	12.2	c	A
133	[Nal(1)10]MS10	1352.6	1352.7	13.5	c	A
134	[Trp10]MS10	1341.5	1341.6	12	c	A
137	[Nle9]MS10	1259.4	1259.6	15.3	c	A

138	[Cit9]MS10	1303.4	1303.6	12.2	c	A
140	[Arg(Me)9,NMePhe10]MS10	1330.4	1330.7	21	a	E
141	[D-Tyr1,Arg(Me)9]MS10	1316.9	1316.7	20.2	a	E
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.1	a	E
143	[D-Trp3,Arg(Me)9]MS10	1316.7	1316.7	20.3	a	E
144	des(1-3)-Fmoc-[Arg(Me)9]MS10	1075.2	1075.5	26	a	E
145	des(1-2)-Fmoc-[Arg(Me)9]MS10	1261.2	1261.6	28.6	a	E

[TABLE 3]

146	[10Ψ,CSNH,D-Tyr1]MS10	1318.4	1318.6	21.4	a	C
150	[Tyr6]MS10	1318.4	1318.6	10.2	c	A
151	[Nal(1)6]MS10	1352.6	1352.7	13.5	c	A
152	[Nal(2)6]MS10	1352.6	1352.7	13.6	c	A
153	[Phe(F5)6]MS10	1392.5	1392.6	13.7	c	A
154	[Phe(4F)6]MS10	1320.8	1320.6	12.3	c	A
156	[Cha6]MS10	1308.2	1308.5	13.2	c	A
163	[6Ψ7,CH2NH]MS10	1288.7	1288.7	18.2	a	D
165	[Dap(Gly)9] MS10	1289.8	1289.6	19.2	a	E
166	[6Ψ7,CSNH]MS10	1318.7	1318.6	20.8	a	F
169	[D-Tyr1,Ala3,Arg(Me)9]MS10	1202.1	1201.6	9.0	c	E
170	[D-Tyr1,Ser3,Arg(Me)9]MS10	1218.2	1217.6	8.8	c	E
171	[D-Tyr1,Cha3,Arg(Me)9]MS10	1284.2	1283.7	12.1	c	E
172	[D-Tyr1,Cha6,Arg(Me)9]MS10	1402.9	1322.7	13.1	c	E
173	[D-Tyr1,Ala7,Arg(Me)9]MS10	1410.9	1330.7	12.2	c	E
174	[D-Tyr1,Arg(Me)9,Trp10]MS10	1335.3	1335.7	11.7	c	E
176	[AzaGly7]MS10	1303.3	1303.6	18.9	a	G
181	[D-Tyr1,Cha3,6,Arg(Me)9]MS10	1370.6	1370.6	13.9	c	E
182	[D-Tyr1,Cha3,6,Arg(Me)9,Trp10] MS10	1328.2	1328.7	21.3	a	E
183	[Phe(4NH2)9]MS10	1328.2	1308.6	19.4	a	A
184	[Phe(4-Guanidino)9]MS10	1350.4	1350.6	19.7	a	E
185	[Dap(GnGly)9]MS10	1331.2	1331.6	19.1	a	E
186	[Trp(For)10]MS10	1369.3	1369.6	19.6	a	B
187	[Abu8]MS10	1274.4	1274.6	10.4	c	A
189	[Ala(3-Bzt)10]MS10	1358.4	1358.6	13.4	c	A
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)9] MS10	1284.5	1284.7	19.3	a	H
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)9] MS10	1218.4	1218.6	15.9	a	H
192	[D-Tyr1,Arg(Et)9]MS10	1330.5	1330.7	18.9	a	E
193	[D-Tyr1,Arg(n-Pr)9]MS10	1344.8	1344.7	19.4	a	E
194	[D-Tyr1,Arg(Ac)9]MS10	1345.1	1344.6	18.8	a	E
197	[Phe(3F)10]MS10	1320.6	1320.6	12.2	c	A
198	[Phe(3,4F2)10]MS10	1338.7	1338.6	12.7	c	A
199	[Phe(3,4Cl2)10]MS10	1370.6	1370.6	13.1	c	A
200	[Phe(3CF3)10]MS10	1370.6	1370.6	13.1	c	A
201	[Ala(2-Qui)10]MS10	1353.4	1353.6	9.8	c	A
203	[D-Tyr1,Cha6,Arg(Me)9]MS10	1322.4	1322.7	12.9	c	E
204	[D-Tyr1, Ala7, Arg(Me)9]MS10	1330.4	1330.7	11.7	c	E
205	[D-Tyr1,Thr3,Arg(Me)9]MS10	1231.4	1231.6	9.0	c	E
206	[D-Tyr1,Ile3,Arg(Me)9]MS10	1243.6	1243.7	10.1	c	E
207	[D-Tyr1,Ser4,Arg(Me)9]MS10	1289.5	1289.6	11.7	c	E

[TABLE 4]

208	[D-Tyr1,Thr4,Arg(Me)9]MS10	1303.4	1303.7	12.0	c	E
209	[D-Tyr1,Gln4,Arg(Me)9]MS10	1330.8	1330.7	11.6	c	E
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	1273.7	1273.6	12.3	c	E
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	1330.7	1330.7	11.7	c	E
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	1300.5	1300.7	12.1	c	E
213	[D-Tyr1,Val8,Arg(Me)9]MS10	1302.5	1302.6	10.4	c	E
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	1330.5	1330.7	11.4	c	E
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	1303.4	1303.7	11.9	c	E
216	des(1)-[D-Asn2,Arg(Me)9]MS10	1153.3	1153.6	11.1	c	E
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	1202.4	1202.6	12.3	c	E
218	[N((CH2)3Gn))Gly9]MS10	1302.5	1302.7	18.6	a	L
220	[Arg(Et)9]MS10	1330.7	1330.7	19.5	a	E
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9] MS10	1232.5	1232.6	16.1	a	H
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	1203.5	1203.6	19.3	a	H
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	1039.5	1039.5	11.0	c	E
224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1202.4	1202.6	12.2	c	E
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	1153.6	1153.6	11.1	c	E
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9] MS10	1103.5	1103.6	9.5	c	E
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9] MS10	1117.3	1117.6	9.8	c	E
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	1129.6	1129.6	11.5	c	E
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1229.5	1229.6	9.7	c	E
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	1316.5	1316.7	11.8	c	E
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	1316.3	1316.7	11.7	c	E
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	1317.0	1317.6	21.0	a	H
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9] MS10	1244.1	1244.7	20.9	a	H
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9] MS10	1230.5	1230.6	20.6	a	H
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9] MS10	1202.5	1202.6	20.5	a	H
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.6	1317.6	20.9	a	H
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me) 9]MS10	1317.6	1317.6	20.9	a	H
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	1317.6	1317.6	20.6	a	H
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1104.1	1104.6	19.0	a	H
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1130.1	1130.6	20.3	a	H
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	1188.0	1118.6	20.3	a	H
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7, Arg(Me)9]MS10	1202.9	1203.6	21.2	a	H
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9] MS10	1278.6	1278.6	10.5	c	H
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me) 9]MS10	1328.5	1328.7	12.3	c	H
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me) 9]MS10	1328.7	1328.7	12.3	c	H
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9] MS10	1315.6	1312.6	11.3	c	H

[TABLE 5]

248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10	1312.5	1312.6	11.6	c	H
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10	1312.5	1312.6	11.7	c	H
250	[D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10	1293.4	1293.6	7.8	c	H
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me) 9]MS10	1279.4	1279.6	7.8	c	H
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me) 9]MS10	1202.4	1202.6	8.5	c	H
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9] MS10	1228.4	1228.6	8.6	c	H
254	des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10	1164.4	1164.6	11.8	c	H
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10	1214.5	1214.6	13.7	c	H
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10	1149.3	1149.6	9.5	c	H
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10	1278.5	1278.6	10.9	c	H
258	[D-Pya(3)1,AzaGly7,Arg(Me)9] MS10	1302.3	1302.6	10.1	c	H
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	1225.5	1225.6	10.7	c	H
260	des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10	1025.2	1025.5	13.7	c	I
261	[7Ψ8,CH2NH]MS10	1288.1	1288.7	17.2	a	D
265	des(1-3)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10	997.3	997.5	12.6	c	I
266	des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10	1011.3	1011.5	12.7	c	I
267	des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7,Arg(Me)9]MS10	1039.3	1039.5	14.4	c	I
268	des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)9]MS10	1048.5	1048.5	15.7	c	I
269	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10	986.7	986.5	13.5	c	I
270	Endo-Phe5a-[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	1425.5	1425.7	13.4	c	H
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	10.4	c	H
272	des(1-2)-Acetyl-[AzaGly7,Arg(Me)9]MS10	1082.3	1082.6	12.8	c	H
273	des(1-2)-Amidino-[AzaGly7,Arg(Me)9]MS10	1082.3	1082.6	11.4	c	J
274	des(1-2)-Acetyl-[Ala3,AzaGly7,Arg(Me)9]MS10	967.3	967.5	9.6	c	H
275	des(1-2)-Acetyl-[Arg3,AzaGly7,Arg(Me)9]MS10	1052.2	1052.6	8.5	c	H
276	des(1-2)-Acetyl-[Thr3,AzaGly7,Arg(Me)9]MS10	997.2	997.5	9.4	c	H
277	des(1-3)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10	952.2	952.5	13.4	c	I
278	des(1-3)-Cyclohexanecarbonyl-[AzaGly7,Arg(Me)9]MS10	964.3	964.5	13.2	c	I
279	des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10	1040.2	1040.5	20.1	a	N
281	[D-Tyr1,Pya(2)6,Arg(Me)9]MS10	1317.3	1317.6	7.8	c	E
282	[D-Tyr1,Pya(4)6,Arg(Me)9]MS10	1317.2	1317.6	8.0	c	E

[TABLE 6]

283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1284.3	1284.7	12.3	c	H
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	1232.2	1232.6	8.6	c	H
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.9	c	H
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.2	1279.6	7.7	c	H
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	1290.1	1290.6	11.4	c	H
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	1340.2	1340.7	10.3	c	H
289	des(1)-[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10	1188.2	1188.6	10.0	c	H
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.7	10.9	c	H
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	1317.4	1318.7	12.0	c	H
293	[4Ψ5,CH2NH]MS10	1288.1	1288.7	18.4	a	D
294	[1Ψ2,CH2NH]MS10	1288.4	1288.7	19.2	a	D
295	[2Ψ3,CH2NH]MS10	1288.1	1288.7	18.2	a	D
296	[6Ψ7,CSNH,D-Tyr1,Arg(Me)9] MS10	1332.1	1332.6	20.5	a	F
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9] MS10	1331.2	1330.7	11.3	c	H
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	1331.1	1330.7	11.6	c	H
299	[1Ψ2,CH2NH,AzaGly7,Arg(Me)9] MS10	1303.4	1330.7	11.3	c	D+H
300	[1Ψ2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9]MS10	1303.4	1303.7	10.8	c	D+H
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1329.4	1329.6	9.0	c	H
302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.6	c	H
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1279.4	1279.6	7.7	c	H
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.4	1165.6	8.0	c	H
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1269.5	1269.5	10.8	c	H
307	[7Ψ8,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.2	1302.7	17.9	a	D+E
308	[6Ψ7,CH2NH,D-Tyr1,Arg(Me)9] MS10	1302.3	1302.7	18.1	a	D+E
310	[Nar9]MS10	1288.8	1288.6	19.4	a	E
311	[Nar(Me)9]MS10	1302.3	1302.6	19.5	a	E
312	[Har(Me)9]MS10	1330.2	1330.7	19.5	a	E
313	[Dab9]MS10	1246.1	1246.6	19.3	a	A
314	[Orn9]MS10	1260.2	1260.6	19.3	a	A
315	des(1)-[D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1121.3	1121.6	11.4	c	H
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1250.5	1250.6	17.0	a	H
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1297.4	1297.6	16.4	a	H
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1335.4	1335.6	19.0	a	H

[TABLE 7]

319	[6Ψ7,NHCO,D-Tyr1,Arg(Me)9] MS10	1316.3	1316.7	18.7	a	K
322	des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10	987.4	987.5	8.1	c	I
323	des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10	962.5	962.5	7.9	c	I
324	des(1-3)-4-Piperidinecarbonyl-[AzaGly7,Arg(Me)9]MS10	965.5	965.5	7.7	c	I
325	des(1-3)-1-Piperidineacetyl-[AzaGly7, Arg(Me)9]MS10	979.5	979.5	8.5	c	I
326	des(1-3)-1-Methylpiperidinio-1-acetyl-[AzaGly7,Arg(Me)9]MS10	993.4	993.6	8.7	c	I
327	des(1-3)-1-Pyridinioacetyl-[Aza Gly7,Arg(Me)9]MS10	973.4	973.5	8.1	c	I
328	des(1-3)-D-Glucronyl-[AzaGly7, Arg(Me)9]MS10	1030.2	1030.5	7.5	c	I
332	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9]MS10	828.6	828.5	9.9	c	H+J
333	des(1-5)-GuAmb-[Arg(Me)9]MS10	827.6	827.5	10.6	c	E+J
334	des(1-5)-GuAmb-[AzaGly7,Arg(Me)9,Trp10]MS10	867.6	867.5	10.3	c	H+J
339	des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10	824.6	824.5	16.0	c	S
340	des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9]MS10	786.4	786.4	8.5	c	S
341	des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9]MS10	757.2	757.4	14.8	c	S
344	des(1-5)-Indole-3-carbonyl-[AzaGly7,Arg(Me)9]MS10	796.5	796.4	14.5	c	S
345	des(1-5)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10	810.5	810.4	15.2	c	S
346	des(1-5)-Ac-[AzaGly7,Arg(Me)9]MS10	695.5	695.4	10.7	c	S
347	des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10	751.7	751.5	16.2	c	S
348	des(1-5)-Z-[AzaGly7,Arg(Me)9]MS10	787.5	787.4	16.7	c	S
349	des(1-5)-Tos-[AzaGly7,Arg(Me)9]MS10	807.5	807.4	15.9	c	S
351	des(1-5)-Benzoyl-MS10	742.4	742.4	15.1	c	A+I
352	des(1-5)-3-(3-Indolyl)propionyl-MS10	809.6	809.4	16.2	c	A+I
353	des(1-5)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	796.4	796.4	15.0	c	S
354	des(1-5)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	863.4	863.5	16.2	c	S

358	des(1-5)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10	734.4	734.4	11.2	c	S
362	des(1-6)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10	638.4	638.4	12.5	c	S
364	des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9]MS10	839.6	839.5	15.8	c	N
366	des(1-5)-n-Hexanoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	790.5	790.5	16.5	c	S
367	des(1-5)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10	826.5	826.4	16.8	c	S
368	des(1-5)-Tos-[AzaGly7,Arg(Me)9,Trp10]MS10	846.6	846.4	16.0	c	S
369	des(1-5)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	878.9	878.5	16.1	c	N

[TABLE 8]

373	des(1-6)-(2S)-2-acethoxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	735.5	735.4	13.6	c	S
374	des(1-6)-Z-[AzaGly7,Arg(Me)9,Trp10]MS10	679.5	679.4	31.2	c	S
375	2-Aminoethyl-Gly-[D-Tyr1,Arg(Me)9]MS10	1416.4	1416.7	17.3	e	E
378	des(1-6)-Diphenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	739.4	739.4	15.9	c	S
379	des(1-6)-(2S)-2-(3-Indolylprpionyloxy)-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	864.7	864.5	18.2	c	S
380	des(1-6)-(2S)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.6	797.4	17.2	c	S
385	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1204.4	1204.6	8.3	c	O
386	des(1-3)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1026.4	1026.2	8.5	c	I
387	Dap-[D-Tyr1,Arg(Me)9]MS10	1402.7	1402.7	17.0	e	E
392	des(1-5)-Benzoyl-[Ala6,AzaGly7,Arg(Me)9,Trp10]MS10	720.5	720.4	11.4	c	S
393	des(1-6)-Dibenzylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	768.7	768.4	16.9	c	P
397	Methylthiocarbamoyl-Sar-[D-Tyr1,Arg(Me)9]MS10	1461.2	1460.7	20.0	e	E
400	(S)-1-(Quinolin-8-yl-carbamoyl)-4-thiapentylcarbamoyl-[D-Tyr1,Arg(Me)9]MS10	1617.9	1617.7	21.7	e	E
408	des(1-6)-1-Oxo-isochroman-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	719.1	719.4	11.3	c	S

412	des(1-6)-(2R)-2-Benzoyloxy-3-phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	796.8	797.4	17.1	c	S
417	des(1-6)-Benzylphenethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	782.9	782.4	17.8	c	P
421	des(1-5)-Benzoyl-[6Ψ7,CH2O,Arg(Me)9,Trp10]MS10	782.2	782.4	22.1	e	Q
423	des(1-5)-Benzoyl-[6Ψ7,NHCO,Arg(Me)9,Trp10]MS10	795.4	795.4	19.8	e	I+K
428	des(1-6)-Dibenzylaminocarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	783.8	783.4	17.0	c	P
431	des(1-5)-Benzoyl-[AzaPhe6,AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	15.3	c	U
432	des(1-5)-3-(3-Pyridyl)propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	9.2	c	S
434	des(1-7)-Dibenzylaminocarbamoylacetyl-[Arg(Me)9,Trp10]MS10	767.6	767.4	14.5	e	R
435	des(1-5)-2-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.7	797.4	14.1	c	S
436	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	797.8	797.4	8.8	c	S
437	des(1-5)-Propionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	748.7	748.4	14.4	c	S
438	des(1-5)-Isobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10	762.4	762.4	13.7	c	S
439	des(1-5)-Cyclohexanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	802.6	802.5	16.3	c	S

[TABLE 9]

440	des(1-5)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	810.1	810.4	15.6	c	S
441	des(1-5)-Benzoyl-[Pya(2)6,AzaGly7,Arg(Me)9,Trp10]MS10	797.6	797.4	9.5	c	S
442	des(1-5)-Benzoyl-[Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10	797.6	797.4	9.1	c	S
443	des(1-5)-2-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.6	811.4	9.0	c	S
444	des(1-5)-5-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.5	811.4	9.2	c	S
445	des(1-5)-6-Methylnicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.4	811.4	8.6	c	S
446	des(1-5)-Pyrazinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	798.4	798.4	12.4	c	S
447	des(1-5)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	765.9	766.5	13.0	c	S
448	des(1-5)-Trifluoroacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	788.6	788.4	14.6	c	S
449	des(1-5)-Benzoyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10	802.6	802.5	17.2	c	S
450	des(1-5)-Benzyl-[AzaGly7,Arg(Me)9,Trp10]MS10	782.7	782.4	11.2	c	H+D
451	des(1-5)-Cyclopropanecarbonyl-[Cha6,AzaGly7,Arg(Me)9,Trp10]MS10	765.9	766.5	15.1	c	S
452	des(1-5)-(R)-3-hydroxy-2-methylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	777.8	778.4	11.4	c	S
453	des(1-5)-2-Hydroxyisobutyryl-[AzaGly7,Arg(Me)9,Trp10]MS10	777.9	778.4	11.9	c	S
454	des(1-5)-3-Furancarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	786.8	786.4	13.7	c	S
455	des(1-5)-Pyrrole-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	785.7	785.4	13.9	c	S
459	des(1-5)-4-Imidazolecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	786.6	786.4	8.5	c	S
460	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Val8,Arg(Me)9,Trp10]MS10	783.5	783.4	6.7	c	S
461	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9,Nal(2)10]MS10	808.5	808.4	11.1	c	S
462	des(1-5)-6-Hydroxynicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	813.8	813.4	10.2	c	S
463	des(1-5)-6-Chloronicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	831.8	831.4	14.3	c	S
464	des(1-5)-6-(Trifluoromethyl)nicotinoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	865.7	865.4	15.8	c	S
466	des(1-5)-2-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	775.8	775.4	8.9	c	H
467	des(1-5)-Dimethylcarbamoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	763.7	763.4	12.5	c	H+N
468	des(1-5)-1-Azetidinecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	775.4	775.4	12.5	e	H+N
471	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Arg(Me)9]MS10	758.8	758.5	9.1	c	S
472	des(1-5)-4-Aminobenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	811.8	811.4	11.2	c	H
473	des(1-5)-4-Aminomethylbenzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	825.8	825.5	9.5	c	H

[TABLE 10]

474	des(1-5)-Pyrrole-3-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	785.8	785.4	12.2	c	S
475	des(1-5)-Pyrimidine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	12.2	c	S
477	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Orn9,Trp10]MS10	741.6	741.3	8.6	c	G+I
478	des(1-5)-4-Pyridinecarbonyl-[AzaGly7,Har9,Trp10]MS10	797.9	797.4	8.6	c	G+I
479	des(1-5)-Pyrimidine-2-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	11.8	c	S
480	des(1-5)-Pyridazine-4-carbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	798.8	798.4	10.7	c	S
481	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9,Trp10]MS10	1204.8	1204.6	8.2	c	G
486	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Orn9]MS10	1109.6	1109.6	13.6	e	G
487	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Lys9]MS10	1123.5	1123.6	13.5	e	G
488	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har9]MS10	1165.6	1165.6	14.1	e	G
489	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Har(Me)9]MS10	1179.6	1179.6	13.9	e	O
490	des(1)-[D-Tyr2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1165.6	1165.6	7.6	c	H
491	des(1)-[D-Tyr2,D-Pya(4)3,Trp5,AzaGly7,Arg(Me)9,Trp10]MS10	1303.8	1303.6	17.2	e	O
492	des(1)-[D-Tyr2,D-Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.9	1161.6	14.3	e	O
493	des(1)-[D-Tyr2,D-Pya(4)3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10	1191.9	1191.6	14.2	e	O
494	des(1,4)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1090.9	1090.6	8.4	c	O
495	des(1-3)-[D-Tyr4,Pya(4)5,AzaGly7,Arg(Me)9,Trp10]MS10	1003.9	1003.5	7.6	c	O
496	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Arg(Me)9,Trp10]MS10	1209.8	1209.7	10.4	c	E
497	des(1)-[D-Tyr2,D-Pya(4)3,Cha6,Ala7,Arg(Me)9,Trp10]MS10	1223.7	1223.7	10.5	c	E
498	des(1)-[D-Tyr2,D-Pya(4)3,Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.7	1230.7	16.8	c	O
499	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1025.3	1025.5	13.6	c	T
500	des(1-3)-3-Phenylpropionyl-[Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	982.5	982.5	15.1	c	T
501	des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1218.7	1218.6	14.2	e	O
502	des(1)-[D-Tyr2,Pya(4)3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1161.4	1161.6	14.0	e	O

503	des(1)-[D-Tyr2,D-Trp3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1199.3	1199.6	17.8	e	O
504	[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1278.6	1278.5	8.1	c	H
505	des(1-3)-3-Phenylpropionyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1040.0	1039.5	13.9	c	T
506	des(1-3)-3-Phenylpropionyl-[Ile5,AzaGly7,Arg(Me)9,Trp10]MS10	1052.0	1051.6	17.6	c	T
507	des(1-3)-3-Phenylpropionyl-[Trp6,AzaGly7,Arg(Me)9,Trp10]MS10	1064.2	1064.5	13.7	c	T

[TABLE 11]

508	des(1-3)-3-Phenylpropionyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1043.2	1043.5	14.1	c	T
509	des(1-3)-Benzoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	997.8	997.5	12.4	c	T
510	des(1-3)-Ac-[AzaGly7,Arg(Me)9,Trp10]MS10	935.9	935.5	9.5	c	T
511	des(1)-[D-Tyr2,D-Trp3,Ala4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1213.6	1213.6	17.9	e	O
512	des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1256.7	1256.6	17.0	e	O
513	des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1213.8	1213.6	18.5	e	O
514	des(1)-[D-Tyr2,D-Phe3,Ala4,AzaGly7,Arg(Me)9,Trp10]MS10	1160.8	1160.6	17.9	e	O
515	des(1)-[D-Tyr2,D-Pya(4)3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1216.8	1216.6	15.7	e	O
	a:0-70% AcCN/35min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	b:0-70% AcCN/35min, flow1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	c:20-70% AcCN/25min, flow1ml/min, YMC ODS AM-301 (4.6 x 100mm)					
	d:5-75% AcCN/35min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	e:0-50% AcCN/25min, flow1ml/min, Wakosil-II 5C18 HG (4.6 x 100mm)					
	Only compound no. 1 represents M+ value.					

The structures of compounds synthesized as in EXAMPLES 1 to 24 and physicochemical properties of these compounds are shown in TABLE 12 below.

[TABLE 12]

Comp. No.		M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode
516	Ac-des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1207.8	1207.6	9.2	c
517	des(1-3)-3-Phenylpropionyl-[Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10	1051.6	1051.5	13.7	c
518	des(1-3)-3-Phenylpropionyl-[Cha6,Arg(Me)9,Trp10]MS10	1030.5	1030.6	15.8	c
519	des(1-3)-Phenylacetyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1011.5	1011.5	12.7	c
521	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7]MS10	1151.5	1151.6	13.4	e
522	des(1-3)-Benzoyl-[Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1011.9	1011.5	12.7	c
523	des(1-3)-Benzoyl-[Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1029.9	1029.5	13.3	c
524	des(1-3)-3-Phenylpropionyl-[Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1036	1035.6	15.8	c
527	des(1)-[D-Tyr2,D-Pya(4)3,Hyp5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.5	1230.6	14.3	c
528	des(1)-[D-Tyr2,D-Pya(4)3,Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1214.7	1214.8	15.7	e
529	des(1)-[D-Tyr2,D-Pya(4)3,Tle5,AzaGly7,Arg(Me)9,Trp10]MS10	1230.7	1230.7	16.5	e
530	des(1)-[D-Tyr2,D-Pya(4)3,Phe5,AzaGly7,Arg(Me)9,Trp10]MS10	1250.6	1250.6	16.8	e
531	des(1-3)-3-Phenylpropionyl-[Pic(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1049.6	1049.6	16.4	c
532	des(1-3)-3-Phenylpropionyl-[Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1021.8	1021.5	14.4	c
533	des(1-3)-3-Phenylpropionyl-[D-Pro5,AzaGly7,Arg(Me)9,Trp10]MS10	1035.7	1035.6	15.2	c
534	des(1-3)-Cyclopropanecarbonyl-[AzaGly7,Arg(Me)9,Trp10]MS10	961.6	961.5	10.7	c
535	des(1-3)-2-Naphthoyl-[AzaGly7,Arg(Me)9,Trp10]MS10	1047.6	1047.5	14.7	c
536	[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1360.3	1360.7	14	e
537	Arg-[Arg1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1516.5	1516.8	13.4	e
538	Arg-[Acp1,D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1473.8	1473.8	13.9	e
539	des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1254.7	1254.7	18.7	e
540	des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10	1242.4	1242.6	11.8	c
541	D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1525.8	1525.8	16.7	e
542	D-Arg-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1681.9	1681.9	16.3	e
545	des(1-3)-Benzoyl-[Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1015.7	1015.5	13	c
546	des(1-3)-3-Phenylpropionyl-[Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10	1067.6	1067.5	15.2	c
547	des(1)-[D-Tyr2,D-Pya(4)3,Ser(Ac)5,AzaGly7,Arg(Me)9,Trp10]MS10	1246.6	1246.7	9.4	c
548	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9,10Ψ,CSNH]MS10	1181.5	1181.6	14.9	e
550	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	13.6	c
551	Ac-D-Arg-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1567.8	1567.8	12.4	c
552	D-Dap-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1455.8	1455.8	11.5	c
553	D-Nle-[Acp1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1482.5	1482.8	13.3	c
554	D-Arg-[b-Ala1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1483.7	1483.8	16.5	e
555	D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1497.7	1497.8	16.6	e
556	D-Arg-D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1654	1653.9	15.7	e
557	D-Arg-D-Arg-D-Arg-[g-Abu1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1809.8	1810	15.6	e
558	Ac-des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9,Trp10]MS10	1284.6	1284.6	13.3	c
559	3-(4-Hydroxyphenyl)propionyl-des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1241.3	1241.6	14.4	c
561	D-Arg-[Acp1,D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1482.8	1482.8	17.5	e
562	Ac-des(1)-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.4	1260.4	15.5	e
563	Ac-des(1)-[D-Tyr2,D-Trp3,Aze(2)5,AzaGly7,Arg(Me)9,Trp10]MS10	1280.6	1280.6	19.1	e
564	Ac-des(1)-[D-Tyr2,D-Trp3,Val5,AzaGly7,Arg(Me)9,Trp10]MS10	1296.5	1296.7	19.9	e
565	Benzoyl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1360.8	1360.7	15.7	c
566	Cyclopropanecarbonyl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1324.8	1324.7	14.5	c
567	Butyryl-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1326.8	1326.7	14.8	c
568	Ac-[D-Arg1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1454.7	1454.7	17.2	e
569	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,6Ψ7,CH2NH,Arg(Me)9,Trp10]MS10	1283.7	1283.7	17.7	e
570	Me-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1270.6	1270.6	16.5	e
571	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9]MS10	1259.5	1259.6	13.2	c
572	des(1)-[D-Trp2,D-Pya(4)3,AzaGly7,Arg(Me)9,Trp10]MS10	1227.6	1227.6	10.1	c
573	Ac-des(1)-[D-Tyr2,D-Trp3,Abu4,AzaGly7,Arg(Me)9,Trp10]MS10	1255.6	1255.6	19.4	e
576	Ac-des(1)-[D-Tyr2,D-Trp3,Gln4,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	18.2	e
577	Ac-des(1)-[D-Tyr2,D-Trp3,Ser4,AzaGly7,Arg(Me)9,Trp10]MS10	1257.7	1257.6	18.8	c
578	Ac-des(1)-[D-Tyr2,D-Trp3,Thr4,AzaGly7,Arg(Me)9,Trp10]MS10	1271.6	1271.6	18.8	e
579	Ac-des(1)-[D-Tyr2,D-Trp3,Alb4,AzaGly7,Arg(Me)9,Trp10]MS10	1299.5	1299.6	19	e
580	Ac-des(1)-[D-Tyr2,D-Trp3,Ser(Me)5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.4	1298.6	19.3	e

Comp. No.	Structure	M+H+ (obs.)	M+H+ (cal.)	HPLC (min.)	HPLC mode	Syn. Proc.
584	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(Ac)4,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	18.7	e	X
585	des(1)-Ac-[D-Tyr2,D-Trp3,Dap(For)4,AzaGly7,Arg(Me)9,Trp10]MS10	1284.7	1284.6	17.9	c	X
586	des(1)-Ac-[D-Tyr2,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10					W
589	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Nal(2)10]MS10	1309.6	1309.6	15.2	c	W
590	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Thi10]MS10	1265.5	1265.6	13.4	c	W
591	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Tyr10]MS10	1275.5	1275.6	12.2	c	W
592	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	1277.5	1277.6	14	c	W
594	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Hph10]MS10	1273.8	1273.6	14.6	c	W
597	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.7	14.1	c	W
598	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Arg(Me)9,Trp10]MS10	1297.5	1297.6	18.5	e	H+W
599	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Orn9,Trp10]MS10	1242.4	1242.6	17.8	c	G+W
600	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Trp10]MS10	1284.7	1284.6	17.9	c	G+W
601	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,D-Phe6,Arg(Me)9,Trp10]MS10	1297.6	1297.6	18.2	c	H+W
602	des(1)-Ac-[D-NMeTyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.7	1312.7	19	c	W
603	des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,D-Phe6,AzaGly7,Arg(Me)9,Trp10]MS1	1260.6	1260.6	15.3	e	W
604	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Tos)9,Trp10]MS10	1438.6	1438.6	20.5	e	G+W
605	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(NO2)9,Trp10]MS10	1329.4	1329.6	18.7	e	G+W
607	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)asym9,Trp10]MS10	1312.9	1312.7	18.1	e	W
608	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me2)sym9,Trp10]MS10	1312.3	1312.7	18.1	c	W
609	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Et)9,Trp10]MS10	1312.8	1312.7	17.7	e	W
610	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys(Me2)9,Trp10]MS10	1284.9	1284.7	17.7	e	G+W
611	des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.9	1260.6	14.4	e	W
612	des(1)-For-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1284.7	1284.6	17.8	e	T+W
613	des(1)-Propionyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.6	1312.7	18.3	e	T+W
614	des(1)-Amidino-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.4	1298.7	16.9	e	J+W
615	des(1)-Ac-[Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1299	1298.6	13.9	c	W
616	des(1)-Ac-[D-Ala2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1206.8	1206.4	13.1	c	W
617	des(1)-Ac-[D-Leu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1248.9	1248.7	15.5	c	W
618	des(1)-Ac-[D-Phe2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1282.7	1282.6	15.8	c	W
619	des(1)-Ac-[D-Nal(1)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1332.6	1332.7	17.6	c	W
620	des(1)-Ac-[D-Nal(2)2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1332.4	1332.7	17.7	c	W
621	des(1)-Ac-[D-Lys2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1263.5	1263.7	11.3	c	W
622	des(1)-Ac-[D-Glu2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1264.6	1264.4	12.7	c	W
623	des(1)-Ac-[D-Tyr2,Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.9	1298.6	14.2	c	W
624	des(1)-Ac-[D-Tyr2,Pya(4)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.8	1260.6	10.2	c	W
625	des(1)-Ac-[D-Tyr2,D-Ala3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1183.8	1183.6	11.4	c	W
626	des(1)-Ac-[D-Tyr2,D-Leu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1226	1225.6	13.3	c	W
627	des(1)-Ac-[D-Tyr2,D-Phe3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1259.9	1259.6	13.8	c	W
628	des(1)-Ac-[D-Tyr2,D-Thr3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1213.9	1213.6	11.1	c	W
629	des(1)-Ac-[D-Tyr2,D-Lys3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1240.9	1240.7	10.1	c	W
630	des(1)-Ac-[D-Tyr2,D-Glu3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1241.9	1241.6	11.2	c	W
631	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Ala6,AzaGly7,Arg(Me)9,Trp10]MS10	1222.9	1222.6	11.6	c	W
632	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Leu6,AzaGly7,Arg(Me)9,Trp10]MS10	1265	1264.7	13.5	c	W
633	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Lys6,AzaGly7,Arg(Me)9,Trp10]MS10	1279.8	1279.7	10.4	c	W
634	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Glu6,AzaGly7,Arg(Me)9,Trp10]MS10	1280.8	1280.6	11.5	c	W
635	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Pya(4)6,AzaGly7,Arg(Me)9,Trp10]MS10	1299.9	1299.6	10.5	c	W
636	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,MePhe6,AzaGly7,Arg(Me)9,Trp10]MS10	1312.4	1312.7	15.4	c	W
637	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1316.5	1316.6	14.4	c	W
638	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Phe(4F)6,AzaGly7,Arg(Me)9,Trp10]MS10	1278.6	1278.6	10.7	c	W
639	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Lys9,Trp10]MS10	1256.9	1256.6	17.5	c	G+W
640	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,D-Leu8,Arg(Me)9,Trp10]MS10	1298.7	1298.6	17.6	e	W
641	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ala8,Arg(Me)9,Trp10]MS10	1256.9	1256.6	16.5	e	W
642	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Val8,Arg(Me)9,Trp10]MS10	1284.5	1284.6	17.4	e	W
643	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Phe8,Arg(Me)9,Trp10]MS10	1332.4	1332.6	18.3	e	W
644	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ser8,Arg(Me)9,Trp10]MS10	1272.9	1272.6	15.5	c	W
645	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har9,Trp10]MS10	1299.1	1298.6	17.7	e	G+W
646	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Har(Me)9,Trp10]MS10	1313.1	1312.7	17.9	e	W
647	des(1)-Ac-[D-Tyr2,D-Trp3,Asp4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1299.9	1299.6	18.2	e	W
648	[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1313.6	1313.7	16	e	W
649	Ac-[Gly1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1355.9	1355.7	17.4	e	W
650	[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1419.8	1419.7	16.6	e	W
651	Ac-[D-Tyr1,D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1461.4	1461.7	18	e	W
652	pGlu-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1367.4	1367.7	17.6	e	W
653	des(1)-Ac-[D-Tyr2,D-Trp3,D-Asn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	18.2	c	W
654	des(1)-Ac-[D-Tyr2,D-Trp3,D-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.6	e	W
655	des(1)-Ac-[D-Tyr2,D-Trp3,MeAsn4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.8	1312.7	18.3	e	W
656	des(1)-Ac-[D-Tyr2,D-Trp3,MeSer5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.8	e	W
657	des(1)-Ac-[D-Tyr2,Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1209.2	1209.6	12.4	c	W
658	des(1)-Ac-[D-Tyr2,D-Pya(2)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.3	1260.6	10.4	c	W
659	des(1)-Ac-[D-Tyr2,D-Trp3,allo-Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.8	1298.6	17.9	c	W
660	des(1)-Ac-[D-Tyr2,D-Pya(3)3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1260.8	1260.6	10.3	c	W

661	des(1)-Ac-[D-Tyr2,D-Pro3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1209.8	1209.6	11.5	c	W
662	des(1)-Ac-[D-Tyr2,Tic3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1271.4	1271.4	13.9	c	W
663	des(1)-Ac-[D-Trp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1321.7	1321.7	15.9	c	W
664	des(1)-Ac-[Tyr2,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1298.7	1298.6	14.1	c	W
665	des(1-2)-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1093.7	1093.6	11.1	c	O
666	des(1-2)-Ac-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1135.7	1135.6	13.4	c	T+W
667	des(1-2)-Hexanoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1191.4	1191.6	17.2	c	T+W
668	des(1-2)-Cyclohexanecarbonyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS	1203.3	1203.6	17.1	c	T+W
669	des(1-2)-Benzoyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1197.8	1197.6	16	c	T+W
670	des(1-2)-3-Pyridinepropionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS1	1226.7	1226.6	11.5	c	T+W
671	des(1-2)-Adipionyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1221.6	1221.6	13.5	c	T+W
672	des(1)-Ac-[D-Tyr2,MeTrp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1312.9	1312.7	14.5	c	W
674	des(1)-Ac-[Acp2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1206.7	1206.7	11.5	c	T+W
675	[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1419.6	1419.7	16.8	e	W
676	Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1461.4	1461.7	18	e	W
677	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Nva8,Arg(Me)9,Trp10]MS10	1284.9	1284.6	17.1	c	W
678	Ac-des(1)-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Ile8,Arg(Me)9,Trp10]MS10	1298.9	1298.6	17.8	c	W
679	des(1-2)-Amidino-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1135.7	1135.5	11.7	c	J+W
680	des(1-2)-Glycoloyl-[D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1151.9	1151.6	12.9	c	W
681	des(1)-Glycoloyl-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,Trp10]MS10	1314.8	1314.6	13.5	c	W
682	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Gln8,Arg(Me)9,Trp10]MS10	1313.9	1313.6	15.7	c	W
685	des(1)-Ac-[D-Tyr2,D-Pya(4)3,Thr5,AzaGly7,Arg(Me)9]MS10	1221.8	1221.6	9.9	c	W
686	des(1)-Ac-[D-Tyr2,D-Trp3,Gly4,AzaGly7,Arg(Me)9,Trp10]MS10	1227.8	1227.6	14.2	c	W
688	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Pya(4)9,Trp10]MS10	1276.8	1276.6	13.9	c	W
689	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Arg(Me)9,D-Trp10]MS10	1298.8	1298.6	13.6	c	W
691	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr6,AzaGly7,Arg(Me)9,Trp10]MS10	1314.4	1314.6	12.3	c	W
692	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Trp6,AzaGly7,Arg(Me)9,Trp10]MS10	1337.5	1337.7	14	c	W
693	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Tyr(Me)6,AzaGly7,Arg(Me)9,Trp10]MS10	1328.9	1328.7	13.9	c	W
694	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Nal(2)6,AzaGly7,Arg(Me)9,Trp10]MS10	1348.9	1348.7	15.7	c	W
695	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Thi6,AzaGly7,Arg(Me)9,Trp10]MS10	1304.7	1304.8	13.6	c	W
696	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Cha6,AzaGly7,Arg(Me)9,Trp10]MS10	1304.9	1304.7	15.3	c	W
698	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,Abu8,Arg(Me)9,Trp10]MS10	1270.7	1270.6	16.7	c	W
699	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,AzaGly7,γMeLeu8,Arg(Me)9,Trp10]MS10	1312.6	1312.7	18.4	e	W
700	des(1)-Ac-[D-Tyr2,D-Trp3,Thr5,Aib8,Arg(Me)9,Trp10]MS10	1269.9	1269.6	16.8	e	E
701	des(1)-Ac-[D-Tyr2,D-Trp3,Dap4,AzaGly7,Arg(Me)9,Trp10]MS10	1257	1256.6	16.7	e	W
702	des(1)-Ac-[D-Tyr2,D-Trp3,Asp(NHMe)4,Thr5,AzaGly7,Arg(Me)9,Trp10]MS	1312.8	1312.7	17.9	c	W

FORMULATION EXAMPLE 1:

(1) Compound No. 305	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 305, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 2

(1) Compound No. 305	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 305 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 3

(1) Compound No. 305	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 305 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 4:

(1) Compound No. 550	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 550, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 5

(1) Compound No. 550	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 550 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 6

(1) Compound No. 550	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 550 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 7:

(1) Compound No. 562	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 562, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 8

(1) Compound No. 562	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 562 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 9

(1) Compound No. 562	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 562 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 10:

(1) Compound No. 571	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 571, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 11

(1) Compound No. 571	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 571 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 12

(1) Compound No. 571	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 571 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 13:

(1) Compound No. 579	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 579, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 14

(1) Compound No. 579	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 579 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 15

(1) Compound No. 579	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 579 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

FORMULATION EXAMPLE 16:

(1) Compound No. 585	10.0 mg
(2) Lactose	60.0 mg
(3) Cornstarch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of Compound No. 585, 60.0 mg of lactose and 35.0 mg of cornstarch is granulated with 0.03 ml of 10% aqueous gelatin solution (3.0 mg as gelatin) through a sieve of 1 mm mesh, dried at 40°C and sieved again. The granules thus obtained are mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablets are coated with sugar-coating of an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets are polished with yellow beeswax to obtain coated tablets.

FORMULATION EXAMPLE 17

(1) Compound No. 585	10.0 mg
(2) Lactose	70.0 mg
(3) Cornstarch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

A mixture of 10 mg of Compound 585 and 3.0 mg of magnesium stearate is granulated with 0.07 ml of an aqueous solution of a soluble starch (7.0 mg as soluble starch), dried, and mixed with 70.0 mg of lactose and 50.0 mg of cornstarch. The mixture is compressed to obtain tablets.

FORMULATION EXAMPLE 18

(1) Compound No. 585	5.0 mg
(2) Salt	20.0 mg

(3) Distilled water to make the whole volume 2 ml

After 5.0 mg of Compound No. 585 and 20.0 mg of salt are dissolved in distilled water, water is added to the solution to make the whole volume 2.0 ml. The solution is filtered and filled in a 2 ml ampoule under aseptic conditions. The ampoule is sterilized and sealed to obtain a solution for injection.

TEST EXAMPLE 1

Assay for hOT7T175 receptor binding activity

(1) Preparation of Cy-5-labeled metastin (40-54)

A synthetic peptide having 40-54 amino acid sequence in the amino acid sequence of metastin, into which Cy-5 was introduced via the ε-amino group of lysine located at the amino terminus and the carboxyl terminus was amidated, was prepared in accordance with the synthesis technique Amersham Bioscience, Inc. Using this synthetic peptide, a test for binding inhibition was carried out.

Sequence: (Cy-5)-KDLPNYNWNSFGLRF-NH_2

(2) Test for binding inhibition using a test compound, Cy-5-labeled metastin (40-54) and h0T7T175-expressed CHO cell

h0T7T175-Expressed CHO cells were cultured in MEM-α medium (nucleic acid-free) containing 10% dialyzed serum. The medium was removed and the adhered cells were washed with PBS. Then, PBS containing 5 mM EDTA was added and the cells were scraped from a flask with a cell scraper.

After centrifugation, the cells were suspended at 1.11×10^5 cells/ml in assay buffer (10 mM HEPES pH 7.4, 140 mM NaCl, 2.5 mM $CaCl_2$, 3 mM $MgCl_2$, 0.5% BSA, 0.01% NaN_3) and Cy-5-labeled metastin (40-54) was added to the suspension in a final concentration of 1 nM. To each well of a 96-Well Black Clear Bottom Microplate (Applied Biosystems, Inc.), 10 μL of assay buffer containing 1% dimethylsulfoxide was added to examine total binding, 10 μL of 10 μM non-labeled peptide (having the same amino acid sequence as that of labeled one) solution diluted with assay buffer to examine non-specific binding, and 10 μL of a test compound diluted with assay buffer to examine a binding inhibition activity of the test compound, and furthermore, 90 μL each of the cell suspension was dispensed to each well. After an hour, the level of Cy-5-labeled metastin (40-54) bound to the cells was determined by the FMAT 8100 HTS system (Applied Biosystems, Inc.). Specific binding is calculated as non-specific binding subtracted from total binding. The binding inhibition activity of a test compound is shown by a ratio of the value obtained by subtracting a measured value in presence of a test compound from the total binding to the specific binding. The receptor binding activity of test compound is shown in TABLES 13 through 18.

[TABLE 13]

Compound Number		IC50(M)
1	Metastin	1.7E-07
3	MS10	6.5E-09
4	des(1)-MS10	2.6E-07
17	[Pya(4)10]MS10	6.6E-12
18	[Tyr(Me)10]MS10	7.7E-09
19	[Phe(2F)10]MS10	8.6E-09
23	[Tyr5]MS10	4.0E-07
24	[Leu5]MS10	8.3E-10
30	Acetyl-MS10	3.1E-08
31	Fmoc-MS10	9.3E-07
32	Leu-Pro-Asn-MS10	2.5E-08
39	[D-Asn4]MS10	8.3E-07
40	[D-Trp3]MS10	1.9E-08
41	[D-Asn2]MS10	2.1E-07
42	[D-Tyr1]MS10	5.7E-08
44	[Lys9]MS10	1.9E-07
50	[Ala7]MS10	1.9E-07
54	des(1-2)-Fmoc-MS10	4.5E-07
57	[Asp2]MS10	1.0E-07
58	[Tyr2]MS10	1.6E-08
59	[Leu2]MS10	3.4E-07
60	[Pya(3)10]MS10	1.7E-07
61	[Phe(4F)10]MS10	1.3E-08
67	[Ala3]MS10	2.7E-08
68	[Leu3]MS10	7.7E-09
69	[Ser3]MS10	8.3E-08
70	[Asp3]MS10	2.0E-07
71	[Lys3]MS10	6.6E-08
72	[Ala1]MS10	5.4E-07
73	[Leu1]MS10	2.2E-07
75	[Asp1]MS10	8.8E-07

[TABLE 14]

77	[Phe(4CN)10]MS10	7.4E-09
78	[Trp(CHO)3, Phe(4CN)10]MS10	2.5E-08
82	[Arg(Me)9]MS10	4.1E-09
83	[Arg(Me2)asy9]MS10	2.5E-08
97	[Har9]MS10	3.7E-07
101	[Ser7]MS10	1.0E-07
105	[Nle8]MS10	8.8E-07
107	[Val8]MS10	1.2E-07
109	[Tyr10]MS10	2.3E-08
110	[Nal(2)10]MS10	2.4E-08
111	[Phe(F5)10]MS10	1.4E-07
112	[Cha10]MS10	3.7E-07
114	des(1-3)-3-(3-Indolyl)propionyl-MS10	5.5E-07
128	[10Ψ,CSNH]MS10	5.5E-08
129	[Arg(Me2)sy9]MS10	8.3E-08
130	[Phe(4Cl)10]MS10	4.2E-08
131	[Phe(4NH2)10]MS10	1.2E-07
132	[Phe(4NO2)10]MS10	9.3E-08
133	[Nal(1)10]MS10	3.3E-07
134	[Trp10]MS10	1.1E-07
141	[D-Tyr1,Arg(Me)9]MS10	5.1E-08
142	[D-Tyr1,D-Trp3,Arg(Me)9]MS10	2.6E-08
143	[D-Trp3,Arg(Me)9]MS10	7.7E-09
145	des(1-2)-Fmoc-[Arg(Me)9]MS10	1.2E-07
146	[10Ψ,CSNH,D-Tyr1]MS10	3.7E-07
150	[Tyr6]MS10	3.2E-07
151	[Nal(1)6]MS10	3.0E-07
152	[Nal(2)6]MS10	1.8E-07
153	[Phe(F5)6]MS10	3.9E-07
154	[Phe(4F)6]MS10	6.0E-08
156	[Cha6]MS10	4.9E-08
163	[6Ψ7,CH2NH]MS10	2.5E-07
166	[6Ψ7,CSNH]MS10	9.4E-09
169	[D-Tyr1,Ala3,Arg(Me)9]MS10	1.6E-07
170	[D-Tyr1,Ser3,Arg(Me)9]MS10	2.6E-07

[TABLE 15]

171	[D-Tyr1,Cha3,Arg(Me)9]MS10	1.1E-07
174	[D-Tyr1,Arg(Me)9,Trp10]MS10	4.2E-07
176	[AzaGly7]MS10	5.2E-08
181	[D-Tyr1,Cha3,6,Arg(Me)9]MS10	1.9E-08
182	[D-Tyr1,Cha3,6,Arg(Me)9,Trp10]MS10	9.8E-08
186	[Trp(CHO)10]MS10	4.6E-07
187	[Abu8]MS10	7.2E-07
189	[Ala(3-Bzt)10]MS10	2.3E-07
190	[D-Tyr1,Cha3,AzaGly7,Arg(Me)9]MS10	1.2E-08
191	[D-Tyr1,Ser3,AzaGly7,Arg(Me)9]MS10	3.0E-07
192	[D-Tyr1,Arg(Et)9]MS10	5.3E-07
193	[D-Tyr1,Arg(n-Pr)9]MS10	9.2E-07
194	[D-Tyr1,Arg(Ac)9]MS10	2.1E-07
197	[Phe(3F)10]MS10	1.7E-07
198	[Phe(3,4F2)10]MS10	1.7E-07
199	[Phe(3,4Cl2)10]MS10	4.7E-07
200	[Phe(3CF3)10]MS10	3.4E-07
201	[Ala(2-Qui)10]MS10	8.2E-07
203	[D-Tyr1,Cha6,Arg(Me)9]MS10	3.7E-08
204	[D-Tyr1, Ala7, Arg(Me)9]MS10	6.8E-07
205	[D-Tyr1,Thr3,Arg(Me)9]MS10	2.6E-07
206	[D-Tyr1,Ile3,Arg(Me)9]MS10	8.5E-08
208	[D-Tyr1,Thr4,Arg(Me)9]MS10	8.3E-07
210	[D-Tyr1,Ala4,Arg(Me)9]MS10	7.3E-07
211	[D-Tyr1,Thr5,Arg(Me)9]MS10	4.4E-08
212	[D-Tyr1,Ala5,Arg(Me)9]MS10	3.6E-08
213	[D-Tyr1,Val8,Arg(Me)9]MS10	1.9E-07
214	[D-Tyr1,Gln2,Arg(Me)9]MS10	3.9E-07
215	[D-Tyr1,Thr2,Arg(Me)9]MS10	2.5E-07
216	des(1)-[D-Asn2,Arg(Me)9]MS10	7.0E-07
217	des(1)-[D-Tyr2,Arg(Me)9]MS10	2.5E-07
220	[Arg(Et)9]MS10	3.3E-07
221	[D-Tyr1,Thr3,AzaGly7,Arg(Me)9]MS10	9.5E-08
222	des(1)-[D-Tyr2,AzaGly7,Arg(Me)9]MS10	3.3E-08
223	des(1-2)-[D-Trp3,Arg(Me)9]MS10	7.6E-07

[TABLE 16]

224	des(1)-[D-Tyr2,D-Trp3,Arg(Me)9]MS10	1.4E-07
225	des(1)-[D-Asn2,D-Trp3,Arg(Me)9]MS10	4.1E-07
226	des(1)-[D-Tyr2,Ser3,Arg(Me)9]MS10	1.0E-07
227	des(1)-[D-Tyr2,Thr3,Arg(Me)9]MS10	4.8E-08
228	des(1)-[D-Tyr2,Ile3,Arg(Me)9]MS10	4.0E-08
229	[D-Tyr1,Val3,Arg(Me)9]MS10	1.3E-07
230	[D-Tyr1,D-Asn2,Arg(Me)9]MS10	2.5E-07
231	[D-Tyr1,D-Asn2,D-Trp3,Arg(Me)9]MS10	5.5E-08
232	[D-Tyr1,AzaGly7,Arg(Me)9]MS10	4.9E-08
233	[D-Tyr1,Ile3,AzaGly7,Arg(Me)9]MS10	2.3E-08
234	[D-Tyr1,Val3,AzaGly7,Arg(Me)9]MS10	4.7E-08
235	[D-Tyr1,Ala3,AzaGly7,Arg(Me)9]MS10	1.0E-07
236	[D-Tyr1,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.2E-08
237	[D-Tyr1,D-Asn2,AzaGly7,Arg(Me)9]MS10	2.7E-08
238	[D-Tyr1,D-Asn2,D-Trp3,AzaGly7,Arg(Me)9]MS10	4.9E-08
239	des(1)-[D-Tyr2,Ser3,AzaGly7,Arg(Me)9]MS10	1.2E-07
240	des(1)-[D-Tyr2,Ile3,AzaGly7,Arg(Me)9]MS10	1.7E-08
241	des(1)-[D-Tyr2,Thr3,AzaGly7,Arg(Me)9]MS10	5.6E-08
242	des(1)-[D-Tyr2,D-Trp3,AzaGly7,Arg(Me)9]MS10	7.0E-08
244	[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	7.7E-08
245	[D-Tyr1,Nal(1)3,AzaGly7,Arg(Me)9]MS10	9.8E-08
246	[D-Tyr1,Nal(2)3,AzaGly7,Arg(Me)9]MS10	7.1E-09
247	[D-Tyr1,Phe(2Cl)3,AzaGly7,Arg(Me)9]MS10	4.5E-08
248	[D-Tyr1,Phe(3Cl)3,AzaGly7,Arg(Me)9]MS10	5.8E-08
249	[D-Tyr1,Phe(4Cl)3,AzaGly7,Arg(Me)9]MS10	1.5E-07
250	[D-Tyr1,Phe(4NH2)3,AzaGly7,Arg(Me)9]MS10	3.7E-09
251	[D-Tyr1,Pya(3)3,AzaGly7,Arg(Me)9]MS10	8.7E-08
252	[D-Tyr1,D-Ala3,AzaGly7,Arg(Me)9]MS10	5.8E-07
253	[D-Tyr1,Pro3,AzaGly7,Arg(Me)9]MS10	2.7E-08
254	des(1)-[D-Tyr2,Phe3,AzaGly7,Arg(Me)9]MS10	1.1E-08
255	des(1)-[D-Tyr2,Nal(2)3,AzaGly7,Arg(Me)9]MS10	3.3E-08
256	des(1)-[D-Pya(3)2,Phe3,AzaGly7,Arg(Me)9]MS10	2.2E-08
257	[D-Tyr1,D-Asn2,Phe3,AzaGly7,Arg(Me)9]MS10	4.0E-08
258	[D-Pya(3)1,AzaGly7,Arg(Me)9]MS10	9.0E-08
259	[D-Ala1,AzaGly7,Arg(Me)9]MS10	2.5E-07

[TABLE 17]

260	des(1-3)-3-(3-Indolyl)propionyl-[AzaGly7,Arg(Me)9]MS10	3.2E-07
261	[7? 8,CH2NH]MS10	3.9E-07
265	des(1-3)-Indole-3-carboxyl-[AzaGly7,Arg(Me)9]MS10	9.5E-08
266	des(1-3)-Indole-3-acetyl-[AzaGly7,Arg(Me)9]MS10	2.3E-07
267	des(1-3)-4-(3-Indolyl)butyryl-[AzaGly7, Arg(Me)9]MS10	3.6E-07
268	des(1-3)-Diphenylacetyl-[AzaGly7,Arg(Me)9]MS10	5.5E-07
269	des(1-3)-3-Phenylpropionyl-[AzaGly7,Arg(Me)9]MS10	4.7E-07
270	Endo-Phe5a-[D-Tyr1,Phe3,AzaGly7,Arg(Me)9]MS10	1.5E-08
271	des(1-2)-[AzaGly7,Arg(Me)9]MS10	1.2E-07
272	des(1-2)-Acetyl-[AzaGly7, Arg(Me)9]MS10	5.4E-07
273	des(1-2)-Amidino-[AzaGly7, Arg(Me)9]MS10	3.0E-07
275	des(1-2)-Acetyl-[Arg3,AzaGly7,Arg(Me)9]MS10	4.1E-07
276	des(1-2)-Acetyl-[Thr3,AzaGly7,Arg(Me)9]MS10	4.8E-07
277	des(1-3)-n-Hexanoyl-[AzaGly7,Arg(Me)9]MS10	5.4E-08
278	des(1-3)-Cyclohexanecarbonyl-[AzaGly7, Arg(Me)9]MS10	1.1E-07
279	des(1-3)-2-(Indol-3-yl)ethylcarbamoyl-[AzaGly7,Arg(Me)9] MS10	2.9E-08
281	[D-Tyr1,Pya(2)6,Arg(Me)9]MS10	2.3E-07
283	[D-Tyr1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	6.9E-10
284	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9]MS10	3.4E-08
285	[D-Tyr1,Pya(2)3,AzaGly7,Arg(Me)9]MS10	4.0E-08
286	[D-Tyr1,Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.7E-08
287	[D-Tyr1,D-Ser2,AzaGly7,Arg(Me)9]MS10	2.3E-09
288	[D-Tyr1,D-His2,AzaGly7,Arg(Me)9]MS10	7.2E-11
289	[D-Pya(3)2,AzaGly7,Arg(Me)9]MS10-(2-10)	8.4E-09
290	[D-Pya(3)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	1.4E-09
291	[D-Pya(3)1,D-Tyr2,Cha3,AzaGly7,Arg(Me)9]MS10	4.1E-10
294	[1? 2,CH2NH]MS10	3.0E-08
295	[2? 3,CH2NH]MS10	6.8E-07
296	[6? 7,CSNH,D-Tyr1,Arg(Me)9]MS10	1.4E-08
297	[D-Tyr1,Thr5,AzaGly7,Arg(Me)9]MS10	9.3E-10
298	[D-Tyr1,D-Asn2,Thr5,AzaGly7,Arg(Me)9]MS10	2.5E-10
299	[1Ψ2,CH2NH,AzaGly7,Arg(Me)9]-MS10	1.2E-09
300	[1Ψ2,CH2NH,D-Trp3,AzaGly7,Arg(Me)9]-MS10	3.8E-09
301	[D-Tyr1,Ala(2-Qui)3,AzaGly7,Arg(Me)9]MS10	1.5E-08

[TABLE 18]

302	[D-Tyr1,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	7.7E-09
303	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-10
304	[D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9]MS10	5.0E-09
305	des(1)-[D-Tyr2,D-Pya(4)3,AzaGly7,Arg(Me)9]MS10	1.3E-09
306	[D-Pya(4)1,D-Asn2,Cha3,AzaGly7,Arg(Me)9]MS10	4.4E-09
307	[7Ψ8,CH2NH,D-Tyr1,Arg(Me)9]MS10	6.4E-08
308	[6Ψ7,CH2NH,D-Tyr1,Arg(Me)9]MS10	3.5E-07
310	[Nar9]MS10	3.1E-07
311	[Nar(Me)9]MS10	4.7E-07
312	[Har(Me)9]MS10	1.0E-07
313	[Dab9]MS10	6.9E-07
314	[Orn9]MS10	4.7E-07
316	[D-Tyr1,D-Asn2,Thr3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.6E-08
317	[D-Tyr1,D-Asn2,Pya(4)3,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	2.1E-09
318	[D-Tyr1,AzaGly7,Arg(Me)9,Phe(4F)10]MS10	9.9E-10
319	[6Ψ7,NHCO,D-Tyr1,Arg(Me)9]MS10	9.7E-09
322	des(1-3)-3-Pyridylpropionyl-[AzaGly7,Arg(Me)9]MS10	5.4E-08
323	des(1-3)-4-Imidazoleacetyl-[AzaGly7,Arg(Me)9]MS10	2.8E-07
328	des(1-3)-D-Glucronyl-[AzaGly7,Arg(Me)9]MS10	4.7E-07

TEST EXAMPLE 2

Assay for intracellular Ca ion level-increasing activity using FLIPR

In accordance with the method described in JPA 2000-312590, the intracellular Ca ion level-increasing activity was measured using FLIPR.

The stable expression cell line rOT7T175 was obtained by transduction of expression plasmid pAK-rOT175 for animal cell into CHO/dhfr$^-$ cells, using CellPhect Transfection Kit (Amersham Pharmacia Biotech, Inc.). First, 240 μL of Buffer A (attached to CellPhect Transfection Kit) was added to 9.6 μg of plasmid DNA dissolved in 240 μL of distilled water followed by stirring. After the mixture was settled for 10 minutes, 480 μL of Buffer B (attached to CellPhect Transfection Kit) was added to the mixture, which was vigorously stirred to form liposomes containing the DNA. Then, 4 x 10^5 CHO/dhfr$^-$ cells (obtained from ATCC) were inoculated on a 60 mm Petri dish. After culturing the cells in Ham's F-12 medium (Nissui Seiyaku Co., Ltd.) supplemented with 10% fetal bovine serum (BIO WHITTAKER, Inc.) at 37°C for 2

days in 5% carbon dioxide gas, 480 μL of the liposomes were dropwise added to the cells in the Petri dish. After culturing the cells at 37°C for 6 hours in 5% carbon dioxide gas, the cells were washed twice with serum-free Ham's F-12 medium and 3 μL of 15% glycerol was added to the cells in the Petri dish followed by treatment for 2 minutes. The cells were again washed twice with serum-free Ham's F-12 medium followed by incubation in Ham's F-12 medium supplemented with 10% fetal bovine serum at 37°C for 15 hours in 5% carbon dioxide gas. The cells were dispersed by trypsin treatment to recover from the Petri dish. The recovered cells were inoculated on a 6-well plate in 1.25×10^4 cells/well and began to incubate at 37°C in Dulbecco's modified Eagle medium (DMEM) medium (Nissui Seiyaku Co., Ltd.) containing 10% dialyzed fetal bovine serum (JRH BIOSCIENCES, Inc.) in 5% carbon dioxide gas. The plasmid-transfected transformed CHO cells grew in the medium but the non-transfected cells gradually died. The medium was exchanged on Days 1 and 2 to remove the cells died. Approximately 20 colonies of the transformed CHO cells that kept growing on Days 8 to 10 after the incubation were isolated. From the cells in these colonies, cells showing high reactivity with the ligand peptide metastin (hereinafter merely referred to as hOT7T175/CHO) were selected to provide for the following experiment.

The intracellular Ca ion level-increasing activity of the synthetic peptide in hOT7T175/CHO was determined using FLIPR (Molecular Devices, Inc.).

hOT7T175/CHO was subcultured in DMEM supplemented with 10% dialyzed fetal bovine serum (hereinafter abbreviated as dFBS) and provided for the experiment (hereinafter abbreviated as 10% dFBS/DMEM). The hOT7T175/CHO was suspended in 10% dFBS-DMEM in 15×10^4 cells/ml. The suspension was inoculated on a 96-well plate for FLIPR (Black Plate Clear Bottom, Coster, Inc.) at 200 μl each (3.0×10^4 cells/200 μl), followed by incubation at 37°C overnight in a 5% CO_2 incubator. The cells thus incubated were used (hereinafter simply referred to as the cell plate). Then, 21 ml of HANKS/HBSS (9.8 g of HANKS', 0.35 g of sodium hydrogencarbonate, 20 ml of 1M HEPES; after adjusting the pH to 7.4 with 1N sodium hydroxide, the mixture was subjected to sterilization through a filter), 210 μl of 250 mM Probenecid and 210 μl of fetal bovine serum (FBS) were mixed (HANKS/HBSS-Probenecid-FBS).

Furthermore, 2 vials of Fluo3-AM (50 μg/vial) were dissolved in 21 μL of dimethylsulfoxide and 21 μL of 20% Pluronic acid. The resulting solution was added to and mixed with 10 ml of HANKS/HBSS-Probenecid-FBS described above. After the culture medium was removed, the mixture was dispensed onto the cell plate in 100 μl

each/well, followed by incubation at 37°C for an hour in a 5% CO_2 incubator (pigment loading). The peptide was dissolved in dimethylsulfoxide in 1 x 10^{-3} M. The peptide solution was diluted with HANKS'/HBSS containing 2.5 mM Probenecid and 0.2% BSA. The dilution was transferred to a 96-well plate for FLIPR (V-Bottom plate, Coster, Inc.) (hereinafter referred to as a sample plate). After completion of the pigment loading onto the cell plate, the cell plate washed 4 times with wash buffer, which was obtained by adding 2.5 mM Probenecid to HANKS'/HBSS, using a plate washer to leave 100 μL of wash buffer after the washing. The cell plate and the sample plate were set in FLIPR and 0.05 ml of a sample from the sample plate was automatically transferred to the cell plate with the FLIPR device to promote the cell response. A change in intracellular calcium ion level for 180 seconds was measured with passage of time.

The intracellular Ca ion level-increasing activity [specific activity to Metastin (1-54)] is shown in TABLES 19 to 23.

[TABLE 19]

Comp. No.	Specific Act.
Metastin(1-54)	1
Metastin(45-54)	10
17	5
18	1
19	2
24	1
30	10
31	2
32	10
40	30
41	10
42	30
45	1
50	30
53	1
54	5
55	5
56	1
74	1
75	1
76	1
78	10
79	1
87	1
88	1
97	10
98	1/2
101	10
105	1
109	20
110	20
111	3
112	2
114	3
128	10
130	10
131	3
132	10
133	3
134	30
141	10
142	2
143	3
144	1
146	10
151	1
152	5
154	5
156	2
163	1
166	5
169	2
170	1
171	10
172	1
173	1

[TABLE 20]

174	10
176	5
182	5
187	1
189	10
190	10
192	1
193	1/2
194	1
197	10
198	10
199	3
200	10
201	1
203	10
204	5
205	10
206	10
207	1/2
208	1
209	1/2
210	1
211	10
212	10
213	2
214	10
215	10
216	1
217	20
220	5
222	10
224	2
225	1
226	1
227	1
228	5
229	1
230	10
231	1
232	3
233	1
234	1
235	1
236	2
237	3
238	1
241	1
242	2
244	1
245	1
246	2
247	1
248	2
249	1
250	1
254	1
255	1

[TABLE 21]

256	1
257	3
258	2
259	1
260	5
261	1
265	3
266	2
267	2
268	1
269	3
270	1
271	1
272	2
273	5
274	1
277	2
278	2
279	5
281	1/2
284	1
286	2
287	2
288	1
289	1
290	1
291	2
294	10
295	1
296	3
297	1
298	5
299	5
300	5
301	1
302	2
303	5
304	3
305	5
306	2
307	1
308	2
310	3
311	1
312	3
314	1
315	1
316	1
317	1
318	5
319	3
322	1
323	1
332	2
333	1
334	5
339	2

[TABLE 22]

340	1/5
341	2
344	1/2
345	2
346	2
347	1/2
348	1/5
349	1/5
351	1/2
352	1/3
353	10
354	10
358	2
362	1/10
364	1
366	1/3
367	1/5
368	1/2
369	2
373	2
374	1/3
375	2
378	1/2
379	2
380	5
385	10
386	7
387	1
392	1/5
393	1
397	5
400	1
408	1/3
412	1/5
417	1
421	1/3
423	5
428	1/10
431	1
432	2
434	1/10
435	10
436	5
437	2
438	3
439	2
440	1
441	1
442	1/2
443	1/2
444	1/3
445	5
446	1
447	5
448	3
449	5
450	1/3

[TABLE 23]

451	5
452	1
453	1
454	6
455	5
459	2
460	1/3
461	1/3
462	1
463	2
464	1
466	1/3
467	1
468	1
471	1
472	3
473	3
474	5
475	3
477	1/5
478	1/3
479	5
480	1
481	5
486	1/2
487	1
488	1
489	1/2
490	3
491	7
492	5
493	2
494	1/3
495	1/6
496	5
497	2
498	7
499	10
500	1
501	10
502	10
503	10
504	2
505	20
506	1
507	5
508	10
509	20
510	3
511	10
512	30
513	20
514	10
515	10

TEST EXAMPLE 3

Assay for intracellular Ca ion level-increasing activity using FLIPR

The intracellular Ca ion level-increasing activity was measured using FLIPR as in TEST EXAMPLE 2. However, (1) the evaluation in TEST EXAMPLE 2 for measuring a change in intracellular Ca ion level for 180 seconds with passage of time was changed to the evaluation for 40 seconds after initiation of the reaction. Also, (2) indication of the activity is changed to EC_{50}/MS10 EC_{50} from the specific activity to Metastin (1-54).

A part of the evaluation results are shown in TABLE 24.

[TABLE 24]

Comp. No.	Specific Act.
40	1.6
41	2.7
42	1.6
82	1.0
97	2.9
109	2.6
114	4.1
128	0.5
134	0.5
141	1.6
146	1.5
152	1.4
156	0.9
174	2.3
176	1.3
187	1.9
206	4.8
208	7.3
210	9.3
211	1.3
212	1.1
217	3.1
222	2.7
232	3.9
239	6.7
240	4.9
241	5.3
242	1.4
260	4.3
265	4.4
266	6.4

268	4.5
269	3.4
279	6.4
294	0.7
296	5.2
297	5.5
298	1.8
303	6.9
305	2.0
308	2.6
310	2.0
311	6.2
312	4.0
314	4.4
318	2.9
319	3.1
322	5.4
332	4.9
333	5.0
334	1.4
339	5.9
341	2.8
353	0.8
354	0.8
358	5.6
369	4.8
375	5.2
378	10.4
379	3.0
385	0.7
386	2.9
387	5.0
393	5.9
423	5.6

436	1.4
438	3.0
445	4.2
447	1.4
449	4.2
451	2.6
454	2.5
455	4.1
459	7.3
463	4.6
464	10.5
467	4.0
468	5.2
472	3.4
473	4.2
474	3.2
475	4.2
479	2.6
480	8.3
481	2.4
488	5.5
490	6.2
491	1.0
492	1.1
493	2.2
494	8.6
496	0.7
497	1.4
498	1.5
499	1.4
500	3.2
501	1.1
502	1.4
503	0.4

504	6.9
505	0.7
506	1.3
507	1.7
508	1.0
509	2.0
510	3.5
511	0.5
512	0.8
513	0.4
514	0.7
515	1.0
516	3.7
517	1.0
518	10.5
519	2.4
521	2.4
522	1.9
523	1.1
524	1.1
527	3.3
528	1.4
529	1.8
530	3.4
531	1.8
532	1.0
533	9.7
534	5.6
535	0.8
536	1.8
537	4.7
538	3.3
539	1.2
540	0.7

541	2.0
542	1.4
545	1.1
546	1.9
547	2.5
548	1.7
550	0.7
551	1.2
552	2.3
553	1.9
554	1.3
555	1.5
556	2.8
557	3.2
558	0.4
559	0.3
561	1.6
562	1.0
563	0.7
564	0.5
565	0.6
566	0.8
567	0.8
568	0.6
569	0.5
570	0.5
571	1.2
572	0.7
573	0.7
576	0.8
577	0.7
578	0.8
579	0.6
580	0.6

Comp. No.	Spec. Act.
584	0.4
585	0.4
586	0.3
589	2.3
590	1.4
591	1.2
592	1.1
594	2.1
595	11.4
597	0.6
598	0.3
599	0.5
600	0.3
601	3.1
602	2.4
603	1.7
604	6.3
605	3.9
607	2.2
608	2.2
609	0.9
610	1.9
611	1.7
612	0.8
613	0.4
614	0.8
615	0.7
616	1.1
617	2.4
618	1.6
619	1.5
620	1.7
621	1.9
622	2.8
623	0.6
624	1.2
625	2.8
626	2.1
627	1.6
628	4.4
629	3.4
630	4.2
631	2
632	1.1
633	3.4
634	10.5
635	1.4
637	0.8
638	1.7
639	2
641	3.5
642	3.7
643	2.5
644	2.5
645	1.1
646	1.8

647	10.6
648	1.6
649	1
650	0.6
651	0.7
652	0.9
653	1.3
654	2.9
655	4.7
656	2.9
657	1.1
658	0.4
659	0.6
660	1.1
661	8.5
662	0.7
663	0.8
664	0.6
665	1.1
666	1.1
667	1.4
668	1.2
669	0.5
670	0.9
671	3.6
672	2.1
674	2
675	0.8
676	1.4
677	0.3
678	1.1
679	1.8
680	2.5
681	1.2
682	7.3
685	4.8
686	0.6
688	9.7
689	2.3
691	1.1
692	0.7
693	1.5
694	1.7
695	0.7
696	0.5
698	2.2
699	1.3
700	0.8
701	1.4
702	0.6
703	3.7

TEST EXAMPLE 4

Assay for cell growth inhibition activity in hOT7T175-expressed CHO cells

hOT7T175-Expressed CHO cells (hereinafter hOT7T175) was cultured in DMEM supplemented with 10% dialyzed FBS (hereinafter 10% dFBS/DMEM), which was used for the following assay. hOT7T175 was suspended in 10% dFBS/DMEM at 10,000 cells/ml. The cells were plated on a 96 well plate at 100 μL each/well (1,000 cells/well), followed by culturing at 37°C -5% CO_2 incubator overnight. On the following day, the medium was removed and 90 μL of 10% dFBS/DMEM supplemented with 0.5% BSA (hereinafter, 0.5% BSA/10% dFBS/DMEM) was added. Subsequently, 10 μL of a solution of metastin or metastin derivative in 0.5% BSA/10% dFBS/DMEM was added to each well, followed by culturing at 37°C -5% CO_2 incubator for 3 days. After 10 μL of Cell Counting Kit-8 solution (Dojin Chemical Laboratory) was added to each well, incubation was performed at 37°C -5% CO_2 incubator for 4 hours, absorbance was measured at 450 nm.

The cell inhibition activities of Metastin (1-54), Metastin (45-54) and synthetic compound are shown in TABLE 25.

[TABLE 25]

Compound Number	IC50 (M)
305	8. 94E-09
232	9. 67E-09
286	1. 83E-08
303	4. 12E-08
322	7. 19E-08
141	8. 70E-08
1-54	2. 12E-07
45-54	8. 51E-06

*"1-54" and "45-54" represent Metastin(1-54) and Metastin(45-54), respectively.

TEST EXAMPLE 5

Assay for chemotaxis inhibition activity in hOT7T175-expressed CHO cells

hOT7T175-Expressed CHO cells (hereinafter hOT7T175) was cultured in DMEM supplemented with 10% dialyzed FBS (hereinafter 10% dFBS/DMEM), which

was provided for assay. Also a 24-well 6.5 mm Transwell (pore size 8.0 μm) (COSTAR) was treated with fibronectin by the following method. Specifically, 0.5 ml of 1 μg/ml bovine fibronectin (Yagai Co., Ltd.) was added to the upper and lower chambers of Transwell. After the mixture was settled at room temperature for 10 minutes, the fibronectin solution was removed and further air-dried. After hOT7T175 washed with DMEM 3 times, the cells were suspended in DMEM containing 0.5% BSA (hereinafter 0.5% BSA/DMEM) at a density of 2.5 x 10^6 cells/ml. Metastin or a metastin derivative was diluted with 0.5% BSA/DMEM. After 600 μL of 0.5% BSA/DMEM supplemented with 20% FBS (or 0.5% BSA/DMEM for negative control) was added to the lower chamber of Transwell, and 50 μL of the cell suspension and 50 μL of the metastin or a metastin derivative dilution (or 0.5% BSA/DMEM for positive control) were added to the upper chamber. After incubation at 37°C in a 5% CO_2 incubator for 7 hours, the culture medium was removed and the upper side of the filter was wiped with a cotton swap wetted with phosphate-buffered saline to remove all cells on the upper side of the filter. The filter was fixed and stained with DifQuick (International Reagents Corporation) and the cells migrated toward the lower side of the filter were counted. The chemotaxis inhibition activity is shown in FIG. 1.

TEST EXAMPLE 6

Evaluation of tumor growth inhibition activity

The tumor growth inhibition effect of Metastin (1-54) (hereinafter referred to as Metastin) and Compounds (Compound Nos. 305 and 322) in vivo using tumor-bearing mice with human colonic carcinoma-derived cell line SW620.

Alza osmotic pump (0.25 μL/hour, 14 days release, Model 1002) filled with 100 μL each of 1 mM Metastin, 0.1 mM and 1 mM Compounds dissolved in distilled water (Otsuka Joryusui K.K.) and distilled water as a vehicle was subcutaneously embedded into the back of BALB/cAnN-nu mice (6 weeks old, female, Charles River Japan, Inc.) under ether anesthesia to initiate intermittent administration for 14 days. The number of experiments was n = 10 in the Metastin group and the vehicle group and n = 11 in the both Compound groups. On the following day, human colonic carcinoma-derived cell line SW620 (ATCC) was dissolved in 20 mM phosphate buffered saline (pH 7.2)(PBS) containing 200 μL of 0.15M NaCl at a density of 2 x 10^6cells. The resulting solution was subcutaneously injected into the left flank of the mice above. The day when the cells were injected was made Day 0. Tumor was

measured with an electronic caliper every other or 2 other days during Days 4 to 13 from the cell administration, and tumor size was calculated by the equation: (shorter diameter)^2 x longer diameter/2. As shown in FIG. 2, the Metastin group (24 nmol/day/mouse x 14 days) showed a significant effect of tumor growth inhibition on Day 6, when compared to the vehicle group. On the other hand, the Compound No. 322 group showed a significant tumor growth inhibition activity in a 1/10 dose (2.4 nmol/day/mouse x 14 days) of Metastin from Days 6 to 8. Also, the Compound No. 322 group (24 nmol/day/mouse x 14 days) receiving the same dose as that of Metastin showed a significant tumor growth inhibition activity from Days 6 to 11, when compared to the vehicle group and on Day 11, showed a significant tumor growth inhibition activity even when compared with the Metastin group. The foregoing results reveal that Metastin shows the effect of tumor growth inhibition in vivo as well and Compound No. 322 has the effect of tumor growth inhibition of 10 times higher than with Metastin.

The results of Compound No. 305 are also shown in FIG. 3. The Metastin group (24 nmol/day/mouse x 14 days) showed a significant effect of tumor growth inhibition from Days 5 to 7, when compared to the vehicle group. On the other hand, the Compound No. 305 group (2.4 nmol/day/mouse x 14 days) receiving a 1/10 dose as that of Metastin showed a significant tumor growth inhibition activity from Days 5 to 11, when compared to the vehicle group. Furthermore, the Compound No. 305 group (24 nmol/day/mouse x 14 days) receiving the same dose as that of Metastin showed a significant effect of tumor growth inhibition from Days 5 to 9 and on Day 11, when compared to the vehicle group, revealing that Compound No. 305 also shows the in vivo effect of tumor growth inhibition of 10 times higher than with Metastin.

TEST EXAMPLE 7

Effect of elevating sugar level by metastin

In order to study the effect of metastin on sugar level by peripheral administration, an operation was performed in free moving animal to collect blood. Mature Wistar male rats (weighing 210 - 230 g at the time of operation) were anesthetized by intraperitoneal injection of 50 mg/kg pentobarbital. The animal was taped dorsally to the dissection pad and the left jugular vein was exposed. A polyethylene tube SP35 (inner diameter of 0.5 mm, outer diameter of 0.9 mm, Natsume Seisakusho Co., Ltd.) was cut into a length of about 30 cm and filled up with 200

units/ml of heparinated saline. Thereafter, the tube was inserted into the jugular vein to a depth of about 4.5 cm and fixed. The other end of the tube was subcutaneously inserted into the back to expose at the jugular (back).

After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 μl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 μl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or 1 mL saline solution of metastin (17, 80 or 170 nmol) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 μl each 0, 5, 15, 30 and 60 minutes starting from the intravenous injection. The collected blood was centrifuged (13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucose level in blood was measured using Fuji Drychem 3500 (FUJI FILM). As shown in FIG. 4, the Metastin group showed a significant effect ($p<0.005$, $n = 5$) of enhancing glucose level in blood dose-dependently (17-170 nmol/kg) from 5 minutes after the intravenous injection, when compared to the control group. In the blood glucose level, a prolonged period of time (30 minutes at maximum) for enhancing the sugar level accompanied by an increase of the maximum level was noted metastin, as the dose increased.

TEST EXAMPLE 8

Effect of promoting pancreatic glucagon secretion by metastin

In order to study the mechanism of metastin for the effect of enhancing glucose level in blood, effects of metastin on the level of blood glucagon, insulin, corticosterone and thyroid hormone (T3) known to be hormones affecting glucose level in blood were examined. An operation was performed in free moving mature Wistar male rats (weighing 260 - 300 g at the time of operation) to collect blood. After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 μl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 μl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or a saline solution of metastin (80 nmol/mL) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 μl each 1, 3, 5 and 15 minutes starting from the intravenous injection. The collected blood was centrifuged

(13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucagon level in blood was measured using a glucagon kit "Daiichi" (Daiichi Radioisotope Laboratories Ltd.), insulin level in blood using rat insulin [^{125}I] assay system (Amersham Biosciences), corticosterone level in blood using rat corticosterone [^{125}I] assay system (Amersham Biosciences), thyroid hormone (T3) in blood using T-3.RIA beads (Dinabott Co. Ltd.), and glucose level in blood using Fuji Drychem 3500 (FUJI FILM). As shown in FIG. 5, the Metastin group showed a significant effect of enhancing glucagon level in blood 1 minute after the injection, when compared to the control group. The significant effect of enhancing glucagon level continued until 5 minutes after the injection. On the other hand, in the insulin level in blood (FIG. 6), corticosterone level in blood (FIG. 7) and thyroid hormone (T3) level in blood (FIG. 8), no change was noted by the injection of metastin. Based on these results and the observed increase in blood glucagon level followed by blood glucose level (FIG. 9), it was considered that the effect of blood glucose level by intravenous injection of metastin would be induced due to stimulation of glucagon secretion by metastin.

TEST EXAMPLE 9

Effect of elevating sugar level by metastin derivatives

The effect of metastin derivatives KiSS305 (Compound No. 305) and KiSS322 (Compound No. 322) on blood glucose level and blood glucagon level was examined. An operation was performed in free moving mature Wistar male rats (weighing 260-3000 g at the time of operation) in a manner similar to TEST EXAMPLE 1 to collect blood. After the operation, the animal was maintained overnight. Prior to administration of metastin, 300 μl of blood was drawn through a 1 ml tuberculin syringe and a 25-gauge needle (both by Terumo Co., Ltd.). To prevent blood clotting, 3 μl of 300 KIU/ml aprotinin solution containing 3 mg/ml EDTA had previously been filled in the syringe. Otsuka saline or a saline solution of metastin (80 nmol/mL) was intravenously injected in a dose of 1 mL/kg through the tube. Blood was collected from the jugular vein by 300 μl each 2, 5, 15, 30, 45 and 60 minutes starting from the intravenous injection. The collected blood was centrifuged (13,000 rpm, 5 minutes) with a high speed refrigerated centrifuge (MR-150, Tomy Seiko Co., Ltd.) to recover the supernatant (plasma). Glucose level in blood was measured using Fuji Drychem 3500 (FUJI FILM) and glucagon level in blood was measured using a glucagon kit

"Daiichi" (Daiichi Radioisotope Laboratories Ltd.), as in TEST EXAMPLE 1 or 2. As shown in FIG. 10, both compounds showed an increase in the blood glucose level. Also, both compounds showed an increase in the blood glucagon level, as shown in FIG. 11.

TEST EXAMPLE 10

Induction of ovulation by human metastin in immature rat

Equine chorionic gonadotropin (eCG, serotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline (Otsuka Pharmaceutical Co., Ltd.) in a concentration of 100 IU/mL. Using a 1 ml tuberculin syringe and a 26-gauge needle (both by Terumo Co., Ltd.), eCG was subcutaneously injected into the dorsal area of female Wistar rats of 23 days old after birth (Charles River Japan, Inc.) in a dose of 10 IU/animal, during 9:30 to 10:00 AM. Following the eCG injection, the animal was grouped after 47 to 48 hours as shown below, to which groups, each drug was injected.

Group A (5 rats): Human chorionic gonadotropin (hCG, gonadotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline at 100 IU/mL and the solution was subcutaneously injected into the back in a dose of 20 IU/animal.

Group B (5 rats): Human metastin was dissolved in saline at 100 nmol/mL and the solution was subcutaneously injected into the back in a dose of 20 nmol/animal.

Group C (5 rats): Human metastin was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.67 nmol/animal.

Group D (6 rats): Saline was subcutaneously injected into the back in a dose of 200 μL/animal.

After administration of the drugs described above, the animal was sacrificed by decapitation after 24 to 25 hours to recover blood, bilateral oviducts and uterus. In collecting blood, 90 μl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample.

The number of oocytes was counted as follows.

Where retention of oocytes in the oviducal ampulla was confirmed by stereomicroscopic observation of the oviduct, the ampulla was punctured with a syringe with 27-gauge needle for syringe (Terumo) to retrieve the oocytes. After granulosa cells

surrounding the oocytes were removed by trypsin treatment, the number of oocytes was counted. Where retention of oocytes in the oviducal ampulla was not confirmed by stereomicroscopic observation of the oviduct, a 27-gauge needle with the polished tip for syringe was inserted into the tubal ostium and more than 400 μL of saline was flushed into the oviduct and uterine for rinsing. Then, the presence or absence of oocytes in the effluent was observed.

The number of oocytes obtained is shown in TABLE 26.

[TABLE 26]

	Group A	Group B	Group C	Group D
1	36	29	29	0
2	35	56	39	0
3	40	17	32	0
4	42	25	22	0
5	35	32	16	0
Average of Ovulation	37. 6	31. 8	27. 6	0. 00
Standard Deviation	3. 21	14. 65	8. 91	0. 00

In the table, the numbers "1" through "5" represent a number for individual rat.

In Group A, which is a multipurpose superovulation treatment group, ovulation of 37.6 oocytes in average per rat was confirmed. In Groups B and C receiving metastin, ovulation of 31.8 and 27.6 oocytes in average, respectively, were confirmed. Turning to Group D receiving saline, the number of oocytes was 0.6 in average, indicating that voluntary ovulation was little observed in the absence of ovulation stimulation.

The level of estradiol contained in the plasma collected from the rats shown in TABLE 22 was determined by radioimmunoassay (DPC-Estradiol Kit; Diagnostic Products Corporation). The results are shown in FIG. 12.

The results reveal that among Groups A, B and C, there is no difference in the

level of estradiol contained in plasma, showing that the level of estradiol was extremely high only in Group D receiving saline.

The level of progesterone contained in plasma was determined by radioimmunoassay (DPC.Progesterone; Diagnostic Products Corporation). The results are shown in FIG. 13.

The results reveal that the level of progesterone was highest in Group A and in Groups B and C, the blood level was approximately half that of Group A and that the progesterone level was extremely low in Group D.

In general, the major steroid hormone produced in rat mouse and human ovaries is estrogen in the mature phase of ovarian follicle, whereas it is progesterone after ovulation was induced. It is understood actually from the results in FIG. 12 and FIG. 13 that Group D receiving saline maintained the state where estrogen was highly produced, because of no induction of ovulation; whereas in Group A receiving hCG, production of estrogen increased. In Groups B and C, which are groups receiving Metastin, the plasma estrogen level was very low but the level of progesterone increased, indicating that metastin induced ovulation in the rat ovary via its normal ovulatory process. It is also considered that since the progesterone level in Groups B and C was lower than in Group A, metastin would have a milder ovarian stimulation.

TEST EXAMPLE 11

Gonadotropin-releasing effect of human metastin in immature rat

Human metastin dissolved in saline in a concentration of 33.3 nmol/mL was subcutaneously injected into the dorsal area of female Wistar rats of 25 days old after birth (Charles River Japan, Inc.) in a dose of 200 µL/animal, i.e., 6.67 nmol as human metastin, during 9:00 to 10:00 AM. Prior to the metastin injection and 1, 2 and 4 hours after the injection, the animal was decapitated to recover blood. In recovery of blood, 90 µl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a centrifuging tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample. The levels of FSH (follicle-stimulating hormone), LH (luteinizing hormone) and progesterone contained in the plasma were determined by radioimmunoassay (Rat Follicle Stimulating Hormone (rFSH) [^{125}I] Biotrack Assay System with Magnetic Separation, Rat Luteinizing Hormone (rLH) [^{125}I] Biotrack

Assay System with Magnetic Separation, both by Amersham Bioscience, and DPC.Progesterone by Diagnostic Products Corporation).

The results obtained by monitoring changes in the FSH level in blood from the immature rat by the metastin injection are shown in FIG. 14. One hour after the metastin injection, the blood FSH level began to significantly increase and reached the maximum after 2 hours. While a decrease in the blood FSH level was noted after 4 hours, the FSH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the LH level in blood from the immature rat by the metastin injection are shown in FIG. 15. Similarly to the case of FSH, the blood LH level began to significantly increase 1 hour after and reached the maximum after 2 hours. While a decrease in the blood LH level was noted after 4 hours, the LH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the progesterone level in blood from the immature rat by the metastin injection are shown in FIG. 16. Reflecting the increase of blood LH level, the progesterone level began to increase slowly 1 hour after the metastin injection and showed a significantly higher level than the level prior to the injection.

The results of FIG. 14 and FIG. 15 reveal that peripheral administration of metastininduces release of gonadotropin such as FSH, LH, etc. The induction of ovulation by metastin demonstrated in TEST EXAMPLE 9 is considered to be mediated by this gonadotropin release, particularly LH release.

The effect of inducing ovulation demonstrated in TEST EXAMPLE 9 is an action in rats receiving eCG but the effect in this TEST EXAMPLE shows the results obtained using nude rats. No eCG pretreatment is required for the effect of releasing gonadotropin by metastin.

The results shown in FIG. 16 mean that the release of gonadotropin by the metastin injection imparts physiological stimulation also to the ovary, resulting in increasing the production of progesterone.

TEST EXAMPLE 12

Gonadotropin-releasing effect of human metastin in mature male rat

Human metastin dissolved in saline in a concentration of 175 nmol/mL was subcutaneously injected into the dorsal area of male Wistar rats of 11 weeks old after birth (Charles River Japan, Inc.) in a dose of 200 μL/animal, i.e., 35 nmol as human

metastin, during 10:30 to 11:30 AM. Prior to the metastin injection and 1, 2 and 4 hours after the injection, the animal was decapitated to recover blood. In recovery of blood, 300 μl of 10 KIU/ml aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a centrifuging tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample. The levels of FSH (follicle-stimulating hormone), LH (luteinizing hormone) and testosterone contained in the plasma were determined by radioimmunoassay (Rat Follicle Stimulating Hormone (rFSH) [^{125}I] Biotrack Assay System with Magnetic Separation, Rat Luteinizing Hormone (rLH) [^{125}I] Biotrack Assay System with Magnetic Separation, both by Amersham Bioscience, and DPC.Total Testosterone by Diagnostic Products Corporation).

The results obtained by monitoring changes in the blood FSH level in rat by the metastin injection are shown in FIG. 17. One hour after the metastin injection, the blood FSH level began to significantly increase and reached the maximum after 2 hours, and even after 4 hours, still maintained a higher state.

The results obtained by monitoring changes in the blood LH level in rat by the metastin injection are shown in FIG. 18. Similarly to the case of FSH, the blood LH level began to significantly increase 1 hour after and reached the maximum after 2 hours. While a decrease in the blood LH level was noted after 4 hours, the LH level was still maintained higher than the level prior to the injection.

The results obtained by monitoring changes in the blood testosterone level in rat by the metastin injection are shown in FIG. 19. The testosterone level showed a rapid increase in 1 hour after the metastin injection. While a decrease in the blood testosterone level was noted after 2 and 4 hours, the testosterone level was still maintained at both points of time higher than the level prior to the injection.

The results of FIG. 17 and FIG. 18 reveal that peripheral administration of metastin induces release of gonadotropin such as FSH, LH, etc. in male rat. In view of the results of TEST EXAMPLE 10, metastin is considered to be an extremely important factor in both female and male rats, in stimulating the release of gonadotropin.

The results shown in FIG. 19 mean that the release of gonadotropin by the metastin injection imparts physiological stimulation also to the testis, resulting in increasing the production of testosterone.

From these results it is considered that administration of metastin would

stimulate the testis mediated by release of gonadotropin. This suggests that metastin possibly affects the male reproductive function including seminal maturation, hormone secretion, etc.

TEST EXAMPLE 13

Test on stability of Compound in blood

Blood was drawn from Balb/c mouse of 8 weeks old (female), settled at 37°C for 30 minutes and centrifuged at 13000 rpm for 10 minutes to give mouse serum. The serum thus obtained was frozen-stored at -80°C.

The stability test was performed by addition of 5 nmol of Compound (5µL of aqueous solution) to 45 µL of serum and then settlement of the mixture at 37°C. The settlement was made at 3 points of time, including 2, 10 and 30 minutes. The sample after the settlement was boiled for 3 minutes and cooled on an ice bath. After 200 µL of acetonitrile/water (3/1) was added to the sample, the mixture was ultrasonicated for 5 minutes and then centrifuged at 5000 rpm for 1 minute. After 150 µL of the supernatant was diluted with 250 µL of distilled water, insoluble matters were removed by filtration through a filter having a pore size of 0.45 µm and 200 µL of the filtrate was applied on HPLC (220 nm) to determine the peak area of Compound. A ratio of the peak area to the area when Compound was treated for 0 minute under the same conditions was calculated as a mean value in 4 respective runs to determine the residual ratio. Next, by taking the calculated residual ratio on the ordinate and time on the abscissa, a graph was prepared and approximated by an exponential function. Thus, the time when the residual ratio reached 50% was calculated as a half life.

The LC-VP series manufactured by Shimadzu Corporation was used as preparative HPLC and Wakosil-II 5C18 HG (4.6 mm x 100 mm) manufactured by Wako Pure Chemical Industries, Ltd. was used as a column. Eluant A (0.1% TFA-containing water) and eluant B (0.1% TFA-containing acetonitrile) were used as eluants. Linear density gradient elution was performed at a flow rate of 1.0 ml/min. using eluants A/B: 100/0 - 0/50 (25 minutes).

Compounds tested and the $t_{1/2}$ (min) values are shown in TABLE 27.

[TABLE 27]

Compound Number	$t_{1/2}$ (min)
1	22.5
3	0.6
42	0.7
82	1.8
134	2.4
141	8.7
232	28.2
286	57.5
296	47.2
305	66.6
308	13.2
319	33.0
322	94.2

TEST EXAMPLE 14

Induction of ovulation in immature rat using metastin derivatives

Equine chorionic gonadotropin (eCG, serotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline (Otsuka Pharmaceutical Co., Ltd.) in a concentration of 100 IU/mL. Using a 1 ml tuberculin syringe and a 26-gauge needle (both by Terumo Co., Ltd.), eCG was subcutaneously injected into the dorsal area of female Wistar rats of 23 days old after birth (Charles River Japan, Inc.) in a dose of 10 IU/animal, during 9:00 to 10:00 AM. Following the eCG injection, the animal was grouped after 47 to 48 hours as shown below, to which groups, each drug was injected.

Group A (5 rats): Human chorionic gonadotropin (hCG, gonadotropin, Dainippon Pharmaceutical Co., Ltd.) was dissolved in saline at 100 IU/mL and the solution was subcutaneously injected into the back in a dose of 20 IU/animal.

Group B (5 rats): Compound No. 305 was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.7 nmol/animal.

Group C (5 rats): Compound No. 305 was dissolved in saline at 10.0 nmol/mL and the solution was subcutaneously injected into the back in a dose of 2.0 nmol/animal.

Group D (5 rats): Compound No. 322 was dissolved in saline at 33.3 nmol/mL and the solution was subcutaneously injected into the back in a dose of 6.7 nmol/animal.

Group E (5 rats): Compound No. 322 was dissolved in saline at 10.0 nmol/mL and the solution was subcutaneously injected into the back in a dose of 2.0 nmol/animal.

Group F (6 rats): Saline was subcutaneously injected into the back in a dose of 200 μL/animal.

After administration of these drugs, the animal was sacrificed by decapitation after 24 to 25 hours to recover blood, bilateral oviducts and uterus. In collecting blood, 90 μl of 10 KIU/mL aprotinin solution (Trasylol, Bayer) containing 3 mg/ml EDTA had been previously filled in a tube for recovery to prevent blood clotting. After blood recovery, the blood was thoroughly blended and the mixture was centrifuged at 2,000G for 25 minutes. After the supernatant was recovered, the product was used as a plasma sample.

The number of oocytes was counted by referring to the method described in Eur. J. Endocrinol., 138, 594-600 (1998).

Where retention of oocytes in the oviducal ampulla was confirmed by stereomicroscopic observation of the oviduct, the ampulla was punctured with a 27-gauge needle for syringe (Terumo) to retrieve the oocytes. After granulosa cells surrounding the oocytes were removed by trypsin treatment, the number of oocytes was

counted. Where retention of oocytes in the oviducal ampulla was not confirmed by stereomicroscopic observation of the oviduct, a with 27-gauge needle with the polished tip for syringe was inserted into the tubal ostium and more than 400 μL of saline was flushed into the oviduct and uterine for rinsing. Then, the presence or absence of oocytes in the effluent was observed.

The number of oocytes thus obtained is shown in FIG. 20. In Group A, which is a multipurpose superovulation treatment group, the number of oocytes was 38.0 oocytes in average per rat. In Groups B, C and D, the number of oocytes was 32.6, 29.4 and 29.6 oocytes in average, respectively, indicating that ovulation was substantially equivalent to Group A. Turning to Group E receiving 2.0 nmol of Compound No. 322, 3 out of 5 rats were ovulated and the number of oocytes was 11.6 in average, which was less than Group A. Further in Group A for negative control, no ovulation was observed.

The results of FIG. 20 reveal that for induction of ovulation equivalent to hCG, at least 2.0 nmol/animal of Compound No. 305 and at least 6.7 nmol/animal of Compound No. 322 should be administered.

The results obtained by measuring the level of estradiol contained in plasma are shown in FIG. 21. The blood estradiol level was measured by radioimmunoassay (DPC.Estradiol Kit, Iatron, Inc.). As shown in FIG. 21, no difference was found among Groups A, B, C and D in terms of estradiol and only Group F showed a high level. Group E had a tendency to show a higher level in rats with no ovulation induction.

The results obtained by measuring the level of progesterone contained in plasma are shown in FIG. 22. The blood progesterone level was measured by radioimmunoassay (DPC.Progesterone, Iatron, Inc.). As shown in FIG. 22, the blood progesterone level was highest in Group A and in Groups B, C and D, the progesterone level shows less than a half of the level in Group A. Groups E and F shows a very low level.

The results of FIG. 21and FIG. 22 reveal that more than 2.0 nmol/animal of Compound No. 305 and more than 6.7 nmol/animal of Compound No. 322 were administered to induce normal differentiation from estrogen-producing granulosa cells to progesterone-producing luteal cells. Furthermore, when Compound No. 305 or KiSS-322 was administered, the progesterone level was lower than in the hCG administration, suggesting that the stimulating effect of these derivatives on ovary would be milder than that of hCG.

TEST EXAMPLE 15

Evaluation of blood testosterone level decreasing effect of metastin peptide derivatives using mature male rat

A metastin peptide derivative (hereinafter peptide) was dissolved in distilled water (Otsuka Joryusui K.K.) to prepare 2 mM peptide solution. This peptide solution was filled in 5 ALZET osmotic pumps (Model 2001, 0.2 ml in volume, release rate: 0.001 ml/hr, DURECT Corporation). The ALZET pumps filled with the peptide solution were implanted subcutaneously in 5 CD(SD)IGS male rats of 9 weeks old after birth (Charles River Japan, Inc.) on the back under ether anesthesia by one pump for one animal. For negative control, distilled water (Otsuka Pharmaceutical Co., Ltd.) was filled in 5 ALZET osmotic pumps, which were similarly implanted in 5 male CD(SD)IGS rats (Charles River Japan, Inc.), respectively. These pump-implanted rats were fed for 6 days under normal feeding conditions. After weighing, the animal was decapitated to collect blood. After 0.03 ml/ml blood of aprotinin solution (Trasylol, Bayer) containing 0.1 mg/ml EDTA.2Na was added to blood, the mixture was centrifuged at 1,800G for 25 minutes to isolate/recover plasma. From the plasma obtained, 0.05 ml was applied to radioimmunoassay (DPC.Total Testosterone Kit, Diagnostic Products Corporation) to measure the plasma testosterone level of each rat. The value below the limit of measurement (0.04 ng/ml of plasma level) in radioimmunoassay was treated as 0. A mean value of the testosterone levels from 5 rats receiving the peptide was calculated and a relative value (percent) of the mean value to a mean value from 5 rats receiving distilled water.

Using this evaluation method, various peptides were evaluated and a part of the results are shown in TABLES 28 and 29.

[TABLE 28]

Comp. No.	Teststerone level in Blood
334	40%
354	43%
436	35%
269	7%
386	23%
499	2%
305	2%
385	2%
492	65%
496	3%
134	50%
141	31%
176	12%

[TABLE 29]

Comp. No.	Teststerone level in Blood
505	40%
508	9%
509	2%
512	2%
515	2%
517	79%

TEST EXAMPLE 16

In a manner similar to TEST EXAMPLE 14, evaluation was made using 0.1 mM peptide solution and a part of the results obtained are shown in TABLE 30.

[TABLE 30]

Compond Number	Teststerone level in Blood
305	48%
385	33%
499	32%
512	38%
516	3%
523	72%
538	45%
540	55%
545	37%
547	65%
550	2%
551	8%
552	21%
553	39%
554	52%
555	73%
558	2%
559	17%
562	11%
564	66%
565	80%
566	89%
567	86%
571	17%

TEST EXAMPLE 17

Evaluation of metastin peptide derivatives for action of reducing testosterone level in blood using mature male rat

Peptide solutions at the concentration of 1 mM was prepared by dissolving the metastin peptide derivatives (hereinafter referred to as peptide) in 50% DMSO aqueous solution. The peptide was encapsulated in five ALZET osmotic pump (Model 2001, 0.2 ml of volume, releasing rate 0.001 ml/hr, DURECT Corporation). The ALZET pumps

encapsulated with the peptide solution were implanted to dorsal subcutaneous of five male CD (SD) IGS rat at nine weeks age (Charles River Japan,Inc.) anesthesized with ether for one pump to one rat. Separately, for negative controls, the ALZET osmotic pumps encapsulated with distilled water were implanted to five male CD (SD) IGS rat (Charles River Japan,Inc.) The rats were bred for six days under the normal conditions. After weighing, blood was collected by decapitation. To 1 ml of blood, 0.03 ml of aprotinin (Trasylol, Byer) solution containing 0.1 g/ml EDTA 2Na was added. The plasma was isolated by centrifugation at 1,800 x g for 25 minutes and collected. The thusobtained plasma, 0.05 ml was effected by radioimmunoassay. (DPC Total Testosterone Kit, Diagnostic Products Corporation) to measure testosterone level in blood of each rat. The value beneath measuring limit of radioimmunoassay (0.04 ng/ml as concentration of plasma) was treated as zero. The mean values for testosterone level of five rats, to which the peptide was given, was calculated and the relative value (percentage) for the mean values of testosterone level of five rats, to which distilled watrer was given, was estimated. One example of the results evaluated for various peptides using this evaluation method was shown in TABLE 31.

[TABLE 31]

Comp. No.	Testosterone level in Blood
305	2%
501	2%
545	2%
548	18%
555	2%
564	2%
589	2%
590	2%
591	2%
592	2%
595	3%
598	2%
599	2%
600	2%
602	2%
608	2%
612	2%
613	2%
615	2%
616	2%
617	2%
618	2%
621	2%
623	2%
625	2%
626	2%
627	2%
629	2%
630	2%
635	2%
637	2%
638	2%
642	2%
648	2%
649	2%
650	2%
651	2%
652	2%
657	2%
658	2%
660	2%
662	2%
663	2%
664	6%
666	2%
667	2%
670	2%
671	2%
672	2%
674	2%
675	2%
676	2%
677	2%

[Sequence Listing Free Text]

SEQ ID NO: 15 The C terminus is amidated.

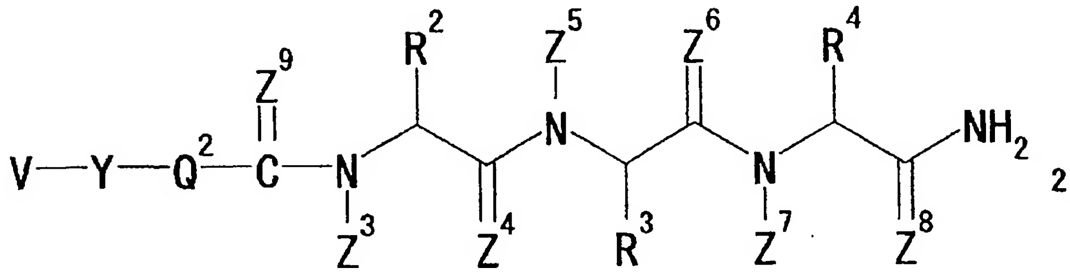
SEQ ID NO: 16 The C terminus is amidated.

SEQ ID NO: 17 The C terminus is amidated.

SEQ ID NO: 18 The C terminus is amidated.

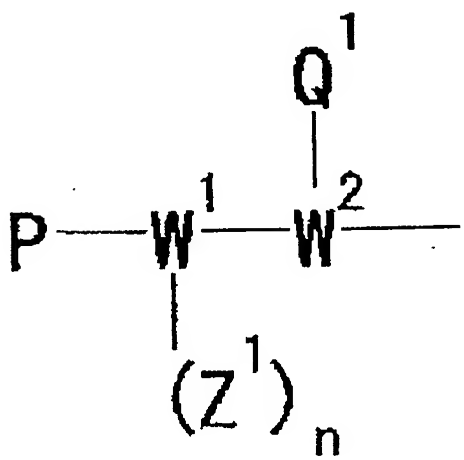
CLAIMS

1. A metastin derivative (II) represented by formula:

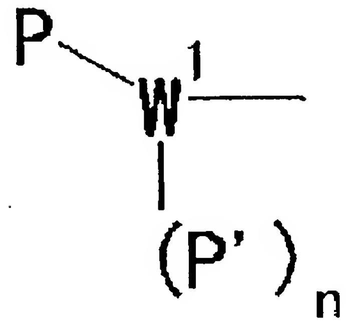


[wherein;

V represents a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that when W^1 is N or CH, n represents 1 and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an

optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO- or $-CH_2CH_2-$, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

$J^1\text{-}J^2\text{-}C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})\text{-}$

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino

group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group, -

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})-$

(wherein:

J^1 and J^2, each has the same significance as defined above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as defined above;

Z^{10} has the same significance as defined above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})-

(wherein:

J^1 and J^2 have the same significance as defined above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as defined above;

Z^{10} has the same significance as defined above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein;

J^1 and J^2 have the same significance as defined above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as defined above; and,

J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

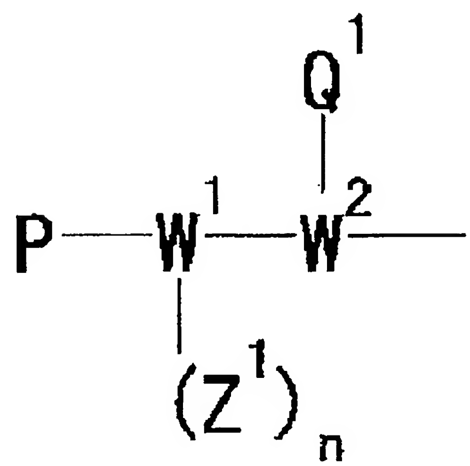
J^1-

(wherein:

J^1 has the same significance as defined above)] (provided that a peptide consisting of the amino acid sequence of 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54,

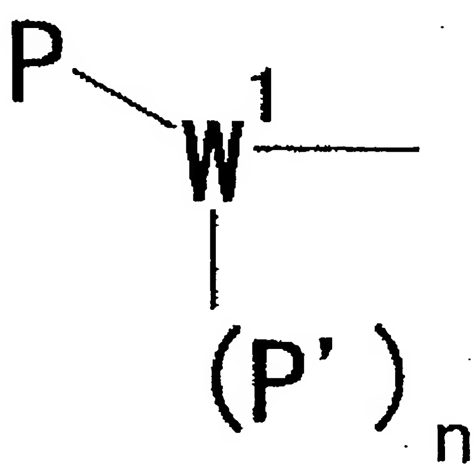
45-54, 46-54, 47-54, 48-54 or 49-54 in the amino acid sequence represented by SEQ ID NO: 1 is excluded), or a salt thereof.

2. The metastin derivative (II) according to claim 1, wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 1), or a salt thereof.

3. The metastin derivative (II) according to claim 1, wherein V is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 1), or a salt thereof.

4. A prodrug of the metastin derivative (II) according to claim 1 or a salt thereof.

5. A pharmaceutical comprising the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

6. The pharmaceutical according to claim 5, which is an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

7. The pharmaceutical according to claim 5, which is an agent for preventing or treating cancer.

8. The pharmaceutical according to claim 5, which is an agent for controlling placental function.

9. The pharmaceutical according to claim 5, which is an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

10. The pharmaceutical according to claim 5, which is an agent for improving gonadal function.

11. The pharmaceutical according to claim 5, which is an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

12. The pharmaceutical according to claim 5, which is an agent for inducing or stimulating ovulation.

13. The pharmaceutical according to claim 5, which is a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

14. The pharmaceutical according to claim 5, which is an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

15. A method for suppressing cancer metastasis or cancer growth, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

16. A method for preventing or treating cancer, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

17. A method for controlling placental function, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

18. A method for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

19. A method for improving gonadal function, which comprises administering

to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

20. A method for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

21. A method for inducing or stimulating ovulation, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

22. A method for promoting gonadotropic hormone secretion or promoting sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

23. A method for preventing or treating Alzheimer's disease or moderate cognitive impairment, which comprises administering to a mammal an effective dose of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof.

24. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing cancer metastasis or an agent for suppressing cancer growth.

25. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating cancer.

26. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for controlling placental function.

27. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or induction of delivery.

28. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for improving gonadal function.

29. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer, infertility, endometriosis, early puberty or myoma of the uterus.

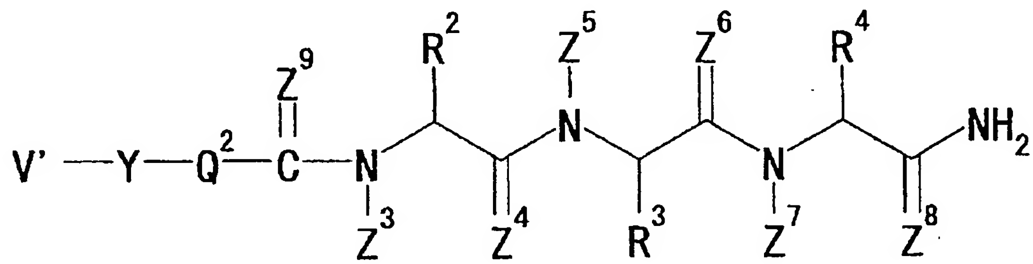
30. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for inducing or stimulating ovulation.

31. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture a gonadotropic hormone secretagogue agent or a sex

hormone secretagogue agent.

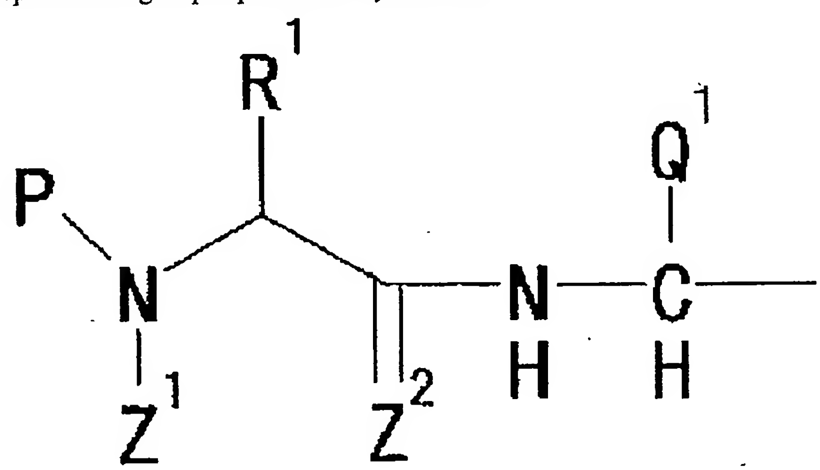
32. Use of the metastin derivative (II) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating Alzheimer's disease or moderate cognitive impairment.

33. An agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion comprising the metastin derivative (III) represented by formula:

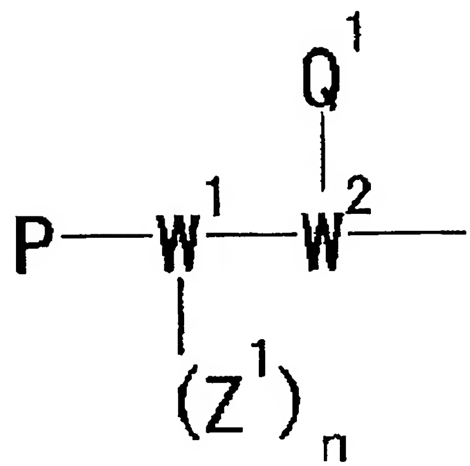


[wherein:

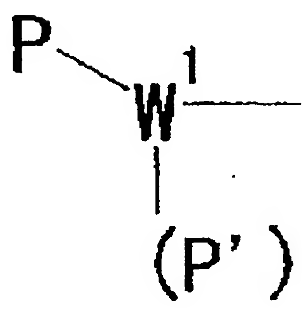
V' represents a group represented by formula:



a group represented by formula:



or a group represented by formula:



n represents 0 or 1;

W^1 represents N, CH or O (provided that W^1 is N or CH, n represents 1, and when W^1 is O, n represents 0);

W^2 represents N or CH;

Z^1, Z^3, Z^5 and Z^7 each represents hydrogen atom or a C_{1-3} alkyl group;

Z^2, Z^4, Z^6 and Z^8 each represents hydrogen atom, O or S;

R^1 represents (1) hydrogen atom, (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group, (3) a cyclic or linear C_{1-10} alkyl group or (4) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group, or (5) an optionally substituted aromatic cyclic group;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group or (4) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group

and an optionally substituted aromatic cyclic group;

R^3 represents (1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent, (2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent, (3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or (4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of (1) an optionally substituted C_{6-12} aromatic hydrocarbon group, (2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (3) an optionally substituted C_{8-14} aromatic fused cyclic group, (4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, (5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and (6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with an optionally substituted C_{1-4} alkyl group with a substituent selected from the group

consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group represented by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$, -COO-, -CSO-, $-CH_2CH_2-$, or –CH=CH-, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S; and,

P and P', which may be the same or different, each may form a ring by combining P and P' or P and Q^1 together and represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C terminus of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein:

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) carbamoyl group, (v) carboxyl group, (vi) sulfino group, (vii) amidino group, (viii) glyoxyloyl group or (ix) amino group, which groups may optionally be substituted with a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

J^3 through J^6 each represents hydrogen atom or a C_{1-3} alkyl group;

Q^3 through Q^6 each represents a C_{1-4} alkyl group, which may optionally have a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused cyclic group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having

carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, Z^1 and R^1, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

Y^1 through Y^3 each represents a group represented by formula:

$-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein J^{13} and J^{14} each represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(wherein:

J^1 and J^2, each has the same significance as defined above;

J^7 through J^9 have the same significance as for J^3;

Q^7 through Q^9 have the same significance as for Q^3;

Y^2 and Y^3 each has the same significance as defined above;

Z^{10} has the same significance as defined above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(wherein:

J^1 and J^2 have the same significance as defined above represents;

J^{10} and J^{11} have the same significance as for J^3;

Q^{10} and Q^{11} have the same significance as for Q^3;

Y^3 has the same significance as defined above;

Z^{10} has the same significance as defined above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula:

J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein;

J^1 and J^2 have the same significance as defined above;

J^{12} has the same significance as for J^3;

Q^{12} has the same significance as for Q^3;

Z^{10} has the same significance as defined above; and

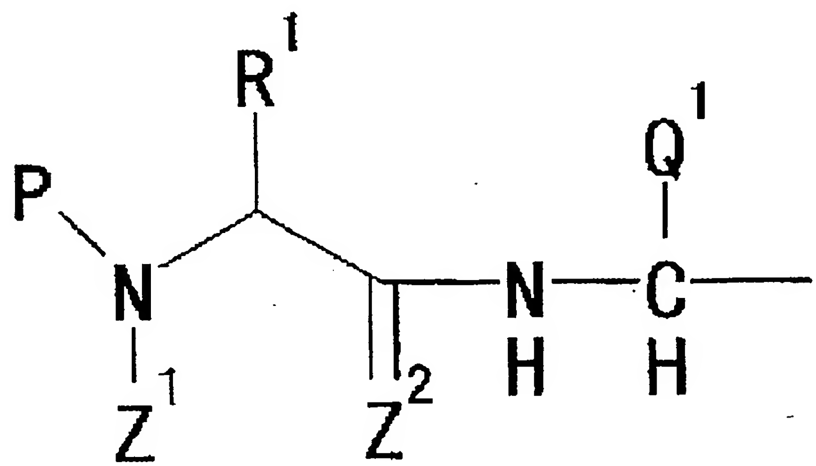
J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula:

J^1- (wherein J^1 has the same significance as defined above)] or a salt thereof, or a prodrug thereof.

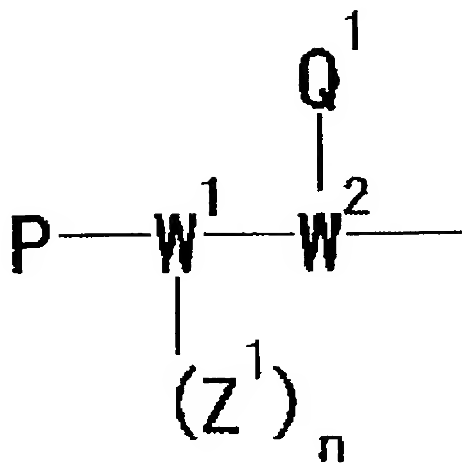
34. The agent according to claim 33, wherein the metastin derivative (III) is the metastin derivative (II) according to claim 1.

35. The agent according to claim 33, wherein V' is a group represented by formula:



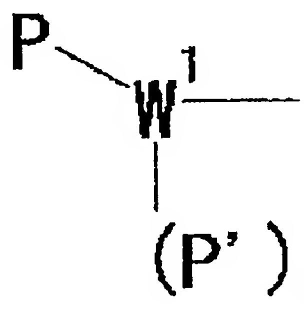
(wherein each symbol has the same significance as defined in claim 33).

36. The agent according to claim 33, wherein V' is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 33).

37. The agent according to claim 33, wherein V' is a group represented by formula:



(wherein each symbol has the same significance as defined in claim 33).

38. The agent according to claims 33 to 37, which is a down-regulating agent for gonadotropic hormone or sex hormone.

39. The agent according to claims 33 to 37, which is a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

40. The agent according to claims 33 to 39, which is an agent for preventing or treating hormone-dependent cancer.

41. A method for suppressing gonadotropic hormone secretion or suppressing sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (III) according to claim 33 or a salt thereof, or a prodrug thereof.

42. A method for down regulating gonadotropic hormone or sex hormone, which comprises administering to a mammal an effective dose of the metastin

derivative according to claim 33 or a salt thereof, or a prodrug thereof.

43. A method for down regulating human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9, which comprises administering to a mammal an effective dose of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof.

44. A method for preventing or treating hormone-dependent cancer, which comprises administering to a mammal an effective dose of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof.

45. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing gonadotropic hormone secretion or an agent for suppressing sex hormone secretion.

46. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for gonadotropic hormone or sex hormone.

47. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture a down-regulating agent for human OT7T175 (metastin receptor) protein consisting of the amino acid sequence represented by SEQ ID NO: 9.

48. Use of the metastin derivative according to claim 33 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing or treating hormone-dependent cancer.

49. A metastin derivative represented by formula:

XX0-XX2-XX3-XX4-XX5-XX6-AzaGly-XX8-XX9-XX10-NH_2

(wherein :

XX0 represents formyl, C_{1-6} alkanoyl, cyclopropanecarbonyl, 6-(acetyl-D-arginylamino)caproyl, 6-((R)-2,3-diaminopropionylamino)caproyl, 6-(D-norleucylamino)caproyl, 4-(D-arginylamino)butyryl, 3-(4-Hydroxyphenyl)propionyl, glycyl, tyrosyl, acetylglycyl, acetyltyrosyl, D-tyrosyl, acetyl-D-tyrosyl, pyroglutamyl, 3-(pyridine-3-yl)propionyl, adipoyl or 6-aminocaproyl;

XX2 represents Tyr, D-Tyr, D-Ala, D-Leu, D-Phe, D-Lys, D-Trp or bond arm;

XX3 represents Trp, Pro, 4-pyridylalanine, Tic, D-Trp, D-Ala, D-Leu, D-Phe, D-Lys, D-Glu, D-2-pyridylalanine, D-3-pyridylalanine or D-4-pyridylalanine;

XX4 represents Asn, 2-amino-3-ureidopropion acid, N^{β}-formyldiaminopropionic acid or N^{β}-acetyldiaminopropionic acid;

XX5 represents Ser, Thr or Val;

XX6 represents Phe, Tyr, Trp, Tyr(Me), Thi, Nal(2), Cha, 4- pyridylalanine or

4-fluorophenylalanine;

AzaGly represents azaglycine;

XX8 represents Leu, Nva or Val;

XX9 represents Arg, Orn, Arg(Me) or Arg(symMe2);

XX10 represents Phe, Trp, 2-naphthylalanine, 2-thienylalanine, tyrosine or 4-fluorophenylalanine), or a salt thereof.

50. D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 305),
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385),
D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 501),
Benzoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 509),
D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 512),
Ac-D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 516),
D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 540),
D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 541),
Benzoyl-Asn-Ser-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 545),
D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-PheΨ(CSNH)NH_2 (Compound No. 548),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 550),
Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),
D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),
D-Nle-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 553),
D-Arg-γ-Abu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 555),
Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),
3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),
Ac-D-Tyr-D-Trp-Asn-Val-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 564),

Cyclopropanecarbonyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 566),
Butyryl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 567),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),
Ac-D-Tyr-D-Trp-Asn-Ser(Me)-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 580),
Ac-D-Tyr-D-Trp-Dap(Ac)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 584),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Thi-NH_2 (Compound No. 590),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Tyr-NH_2 (Compound No. 591),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Orn-Trp-NH_2 (Compound No. 599),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg-Trp-NH_2 (Compound No. 600),
Ac-D-NMeTyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 602),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(symMe2)-Trp-NH_2 (Compound No. 608),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 615),
Ac-D-Ala-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 616),
Ac-D-Leu-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 617),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Lys-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 621),
Ac-D-Tyr-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 623),
Ac-D-Tyr-D-Ala-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 625),
Ac-D-Tyr-D-Leu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 626),

Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627), Ac-D-Tyr-D-Lys-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 629), Ac-D-Tyr-D-Glu-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 630), Ac-D-Tyr-D-Trp-Asn-Thr-Pya(4)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 635), Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637), Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638), Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Val-Arg(Me)-Trp-NH_2 (Compound No. 642), Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 648), Ac-Gly-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 649), D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 650), Ac-D-Tyr-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 651), pGlu-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 652), Ac-D-Tyr-Pro-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 657), Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658), Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660), Ac-D-Tyr-Tic-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 662), Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663), Ac-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 666), Hexanoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 667), 3-Pyridinepropionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 670), Adipoyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 671), Ac-D-Tyr-NMeTrp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 672), 6-Aminocaproyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 674), or salts thereof.

51. Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2

(Compound No. 550),
Ac-D-Arg-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 551),
D-Dap-Acp-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 552),
Ac-D-Tyr-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 558),
3-(4-Hydroxyphenyl)propionyl-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 559),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 562),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 571),
Ac-D-Tyr-D-Trp-Alb-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 579),
Ac-D-Tyr-D-Trp-Dap(For)-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 585),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Nal(2)-NH_2 (Compound No. 589),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 592),
For-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 612),
Propionyl-D-Tyr-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 613),
Ac-D-Phe-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 618),
Ac-D-Tyr-D-Phe-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 627),
Ac-D-Tyr-D-Trp-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 637),
Ac-D-Tyr-D-Pya(4)-Asn-Thr-Phe(4F)-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 638),
Ac-D-Tyr-D-Pya(2)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 658),
Ac-D-Tyr-D-Pya(3)-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 660),
Ac-D-Trp-D-Trp-Asn-Thr-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 663),
or salts thereof.

52. A method of enhancing blood stability, which comprises introducing one or two alkyl groups into the side chain of Arg in the Arg-containing peptide.

53. A method of enhancing blood stability, which comprises introducing one alkyl group into the side chain of Arg in the Arg-containing peptide.

54. A method of enhancing blood stability, which comprises converting the side chain of Arg in the Arg-containing peptide to N^{ω}-alkylated Arg.

55. The method according to claims 52 through 54, wherein an alkyl group is a C_{1-4} alkyl group.

56. The method according to claims 52 through 54, wherein an alkyl group is a methyl group.

57. The method according to claims 52 through 54, wherein an Arg-containing peptide is a peptide having a partial peptide characterized by the structure -Arg-XXX-, wherein XXX represents an amino acid having optionally substituted aromatic ring group into the side chain.

58. The method according to claim 57, wherein XXX is Phe, Trp or Tyr.

FIG 1

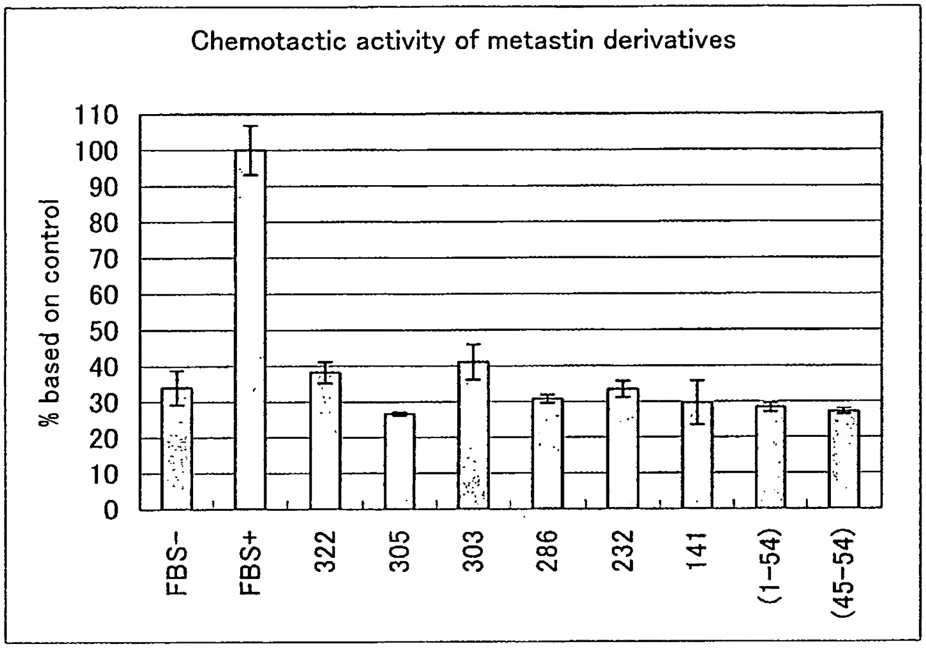

Chemotactic activity of metastin derivatives
% based on control
110
100
90
80
70
60
50
40
30
20
10
0
FBS-
FBS+
322
305
303
286
232
141
(1-54)
(45-54)

FIG 2

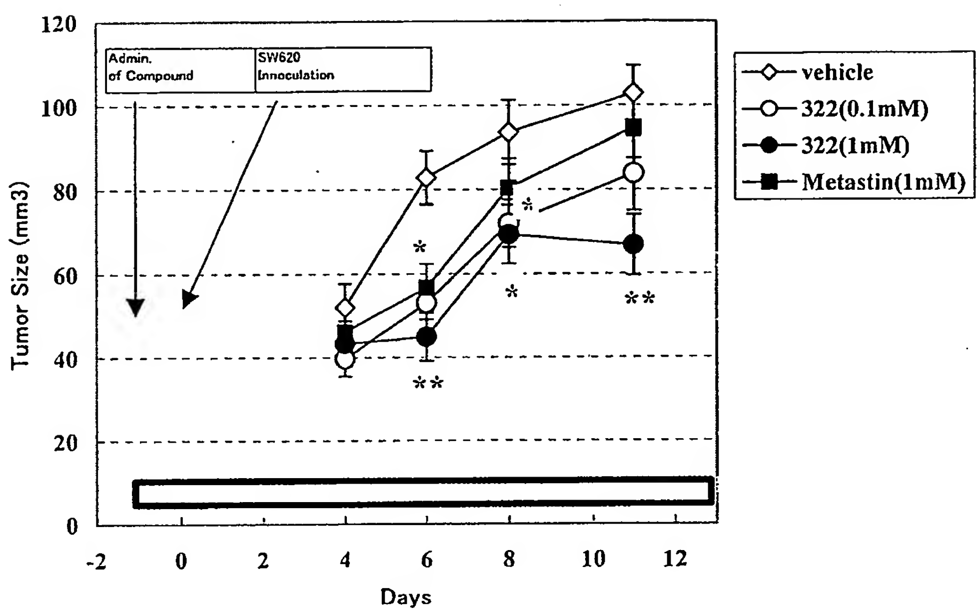

Admin. of Compound
SW620 Innoculation
vehicle
322(0.1mM)
322(1mM)
Metastin(1mM)
Tumor Size (mm3)
Days
120
100
80
60
40
20
0
-2
0
2
4
6
8
10
12
*
**
*
*
**

FIG 3

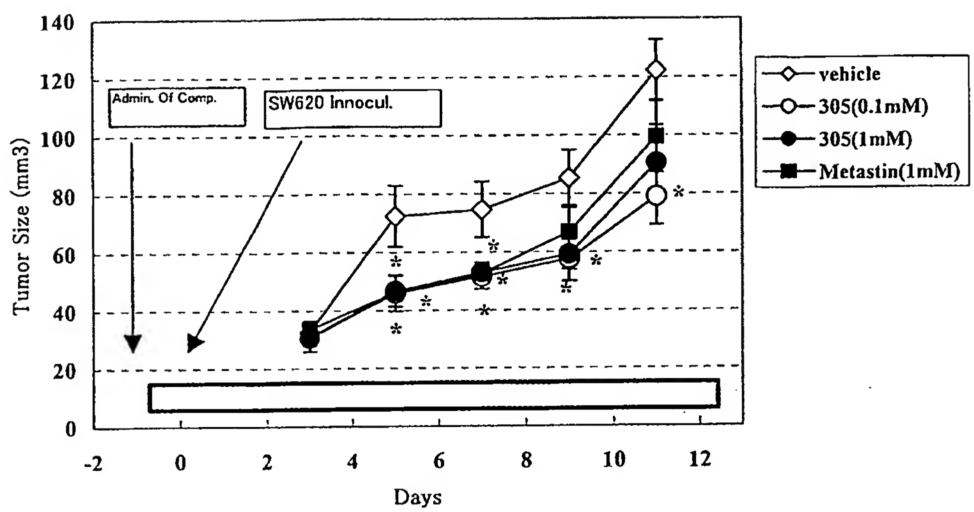

140
120
100
80
60
40
20
0
Tumor Size (mm3)
Admin. Of Comp.
SW620 Innocul.
-2
0
2
4
6
8
10
12
Days
vehicle
305(0.1mM)
305(1mM)
Metastin(1mM)

Fig 4

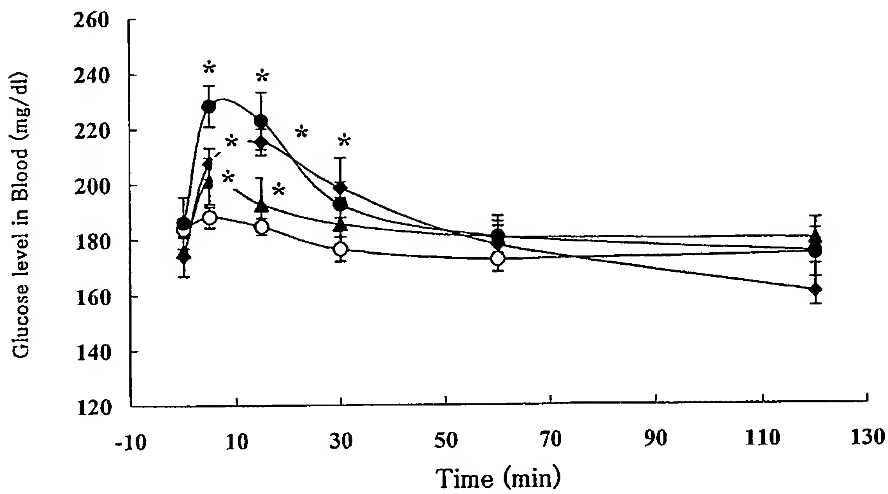

260
240
220
200
180
160
140
120
Glucose level in Blood (mg/dl)
-10
10
30
50
70
90
110
130
Time (min)
*

FIG 5

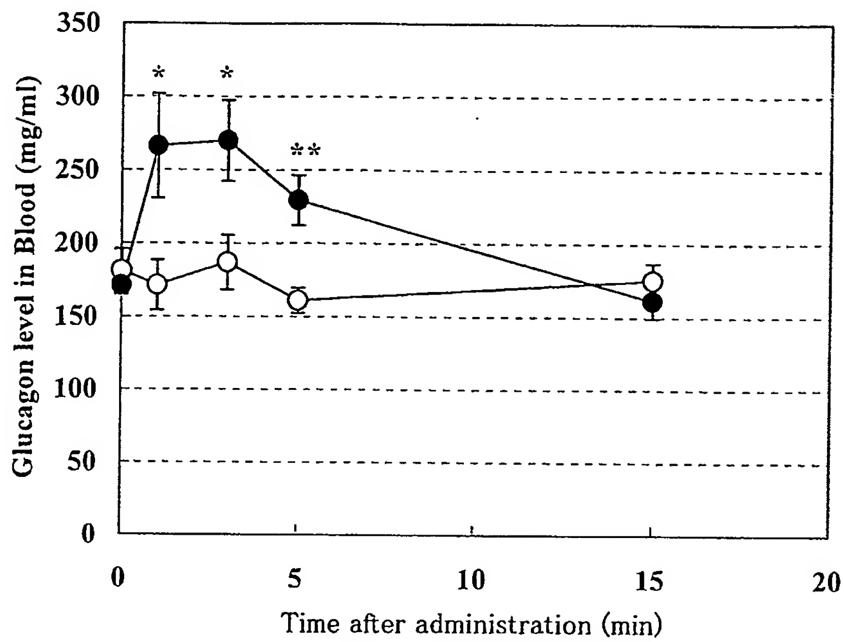

350
300
250
200
150
100
50
0
Glucagon level in Blood (mg/ml)
*
*
**
0
5
10
15
20
Time after administration (min)

FIG 6

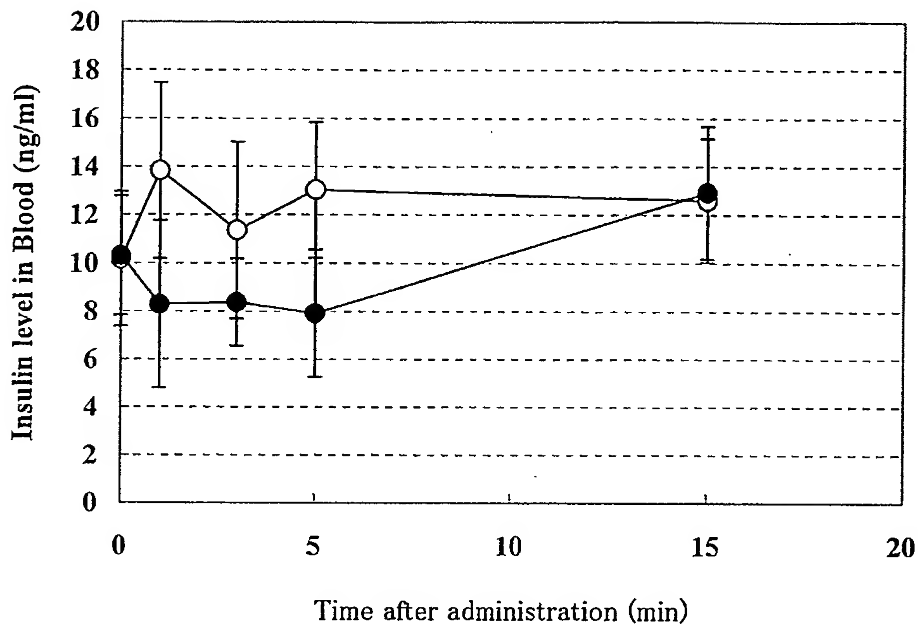

Insulin level in Blood (ng/ml)
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
Time after administration (min)

FIG 7

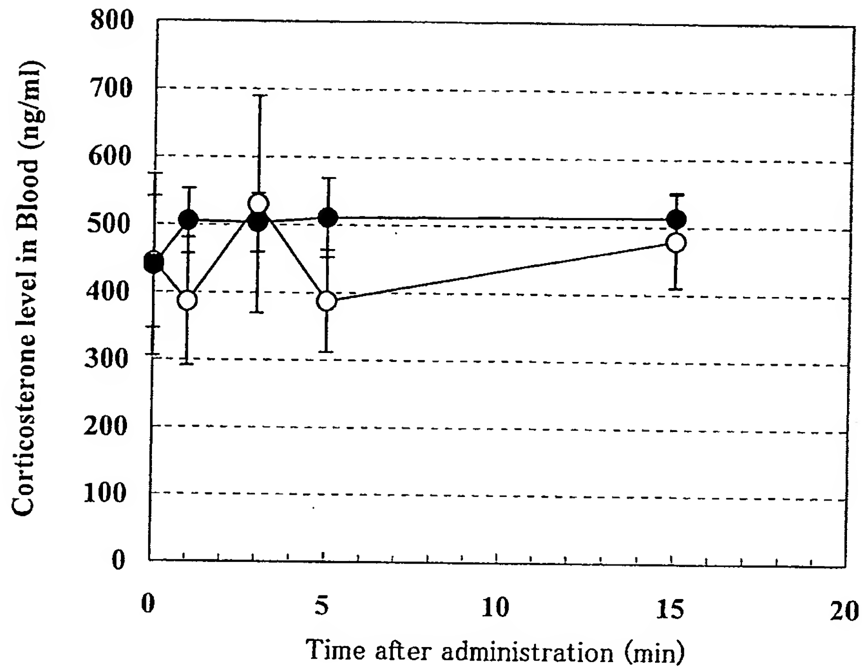

Corticosterone level in Blood (ng/ml)
800
700
600
500
400
300
200
100
0
0
5
10
15
20
Time after administration (min)

FIG 8

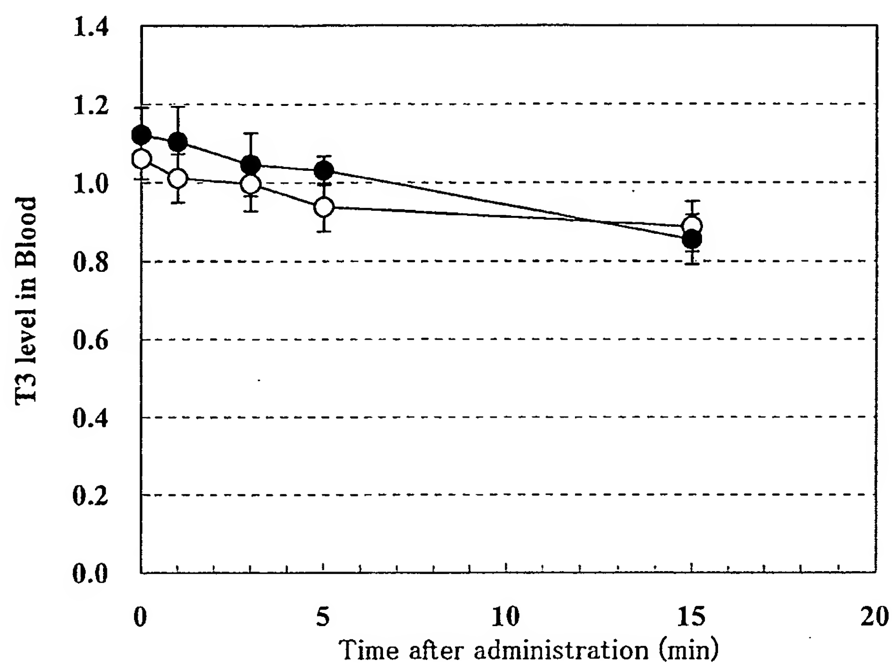

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
T3 level in Blood
0
5
10
15
20
Time after administration (min)

FIG 9

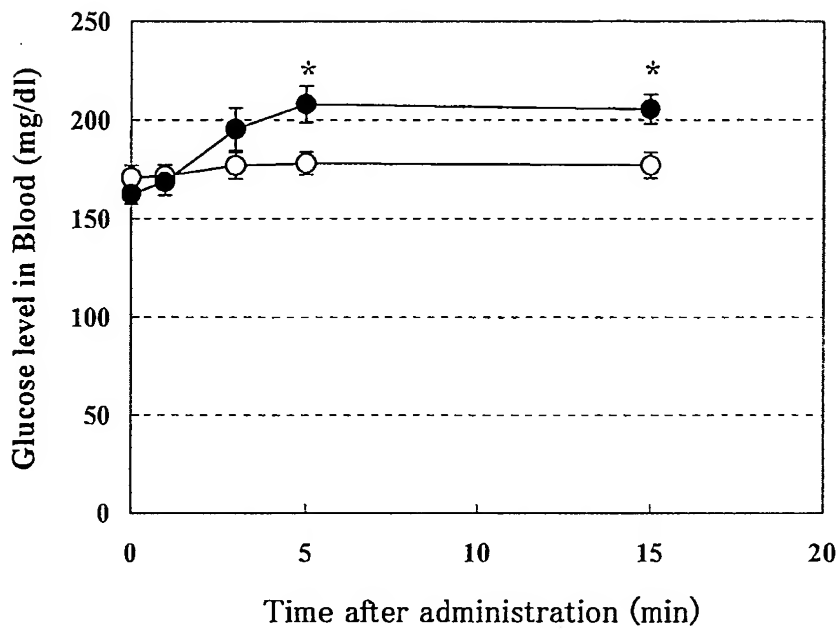

250
200
150
100
50
0
Glucose level in Blood (mg/dl)
*
*
0
5
10
15
20
Time after administration (min)

FIG 10

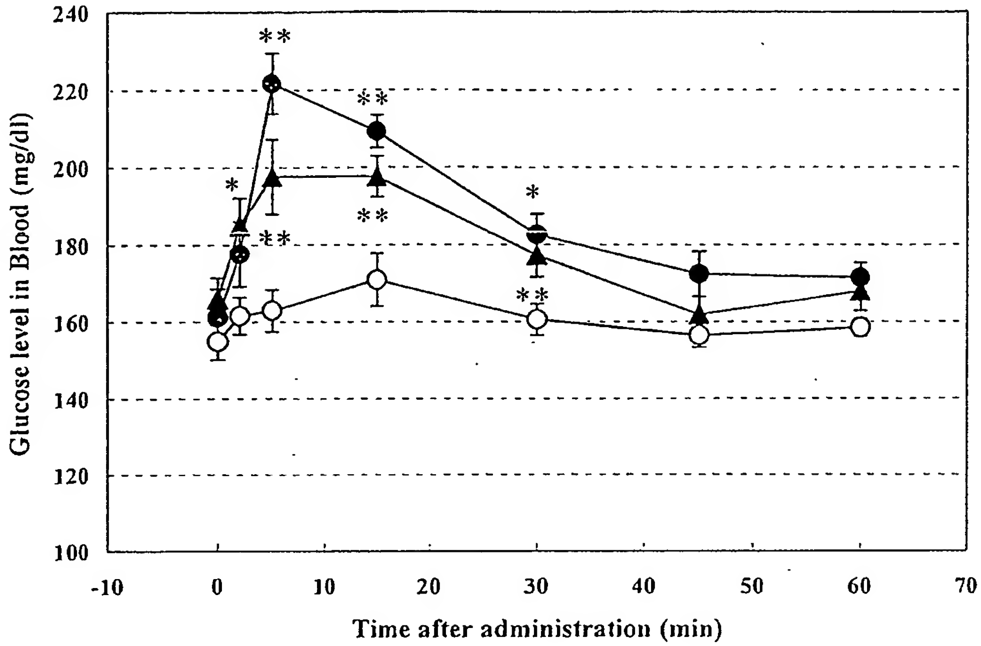

240
220
200
180
160
140
120
100
Glucose level in Blood (mg/dl)
-10
0
10
20
30
40
50
60
70
Time after administration (min)
**
*
*
**
**
**
**

FIG 11

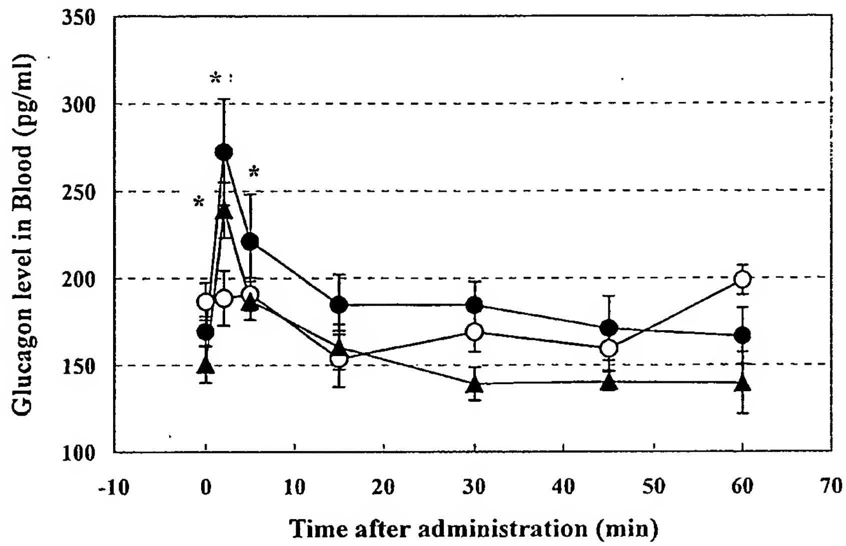

Glucagon level in Blood (pg/ml)
350
300
250
200
150
100
-10
0
10
20
30
40
50
60
70
Time after administration (min)
*
*
*

FIG 12

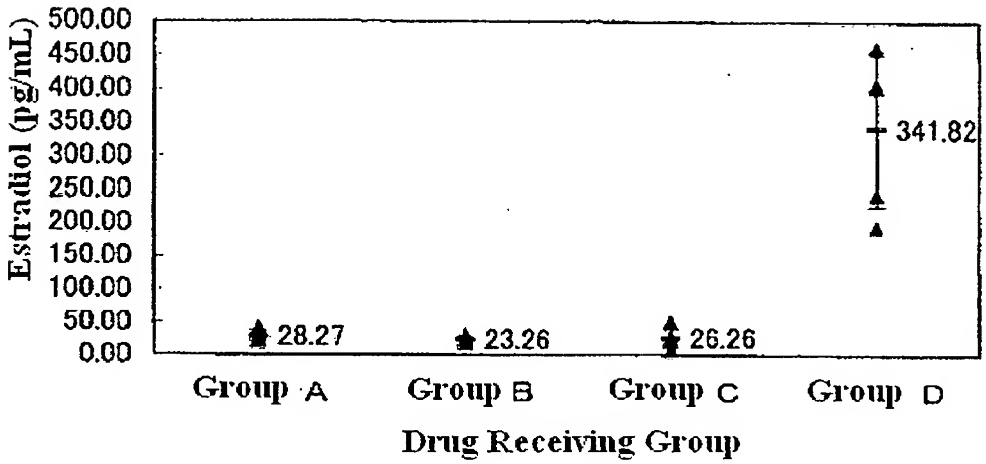

Estradiol (pg/mL)
500.00
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
28.27
23.26
26.26
341.82
Group A
Group B
Group C
Group D
Drug Receiving Group

FIG 13

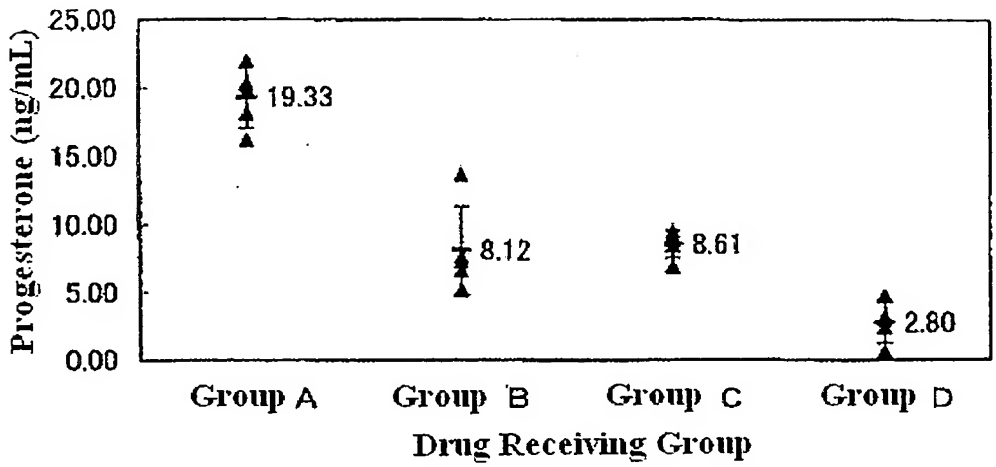

Progesterone (ng/mL)
25.00
20.00
15.00
10.00
5.00
0.00
19.33
8.12
8.61
2.80
Group A
Group B
Group C
Group D
Drug Receiving Group

FIG 14

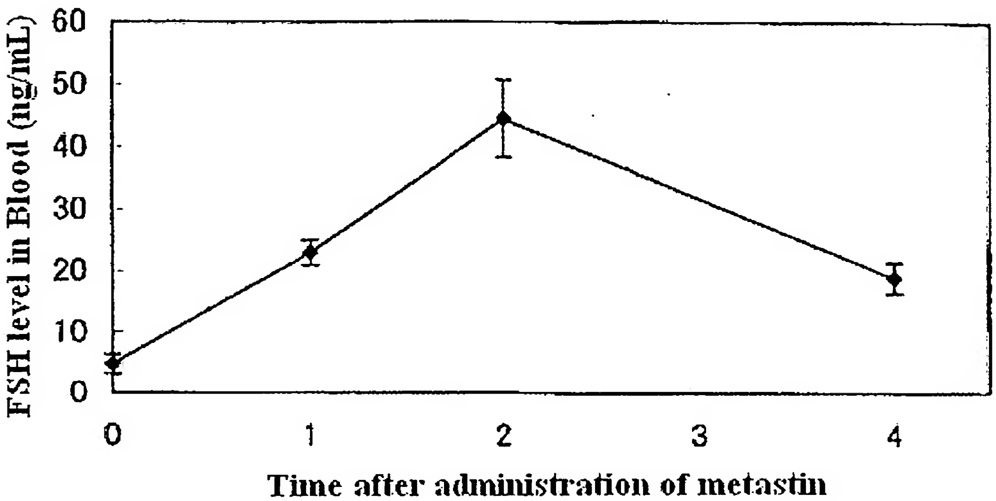

FSH level in Blood (ng/mL)
60
50
40
30
20
10
0
0
1
2
3
4
Time after administration of metastin

FIG 15

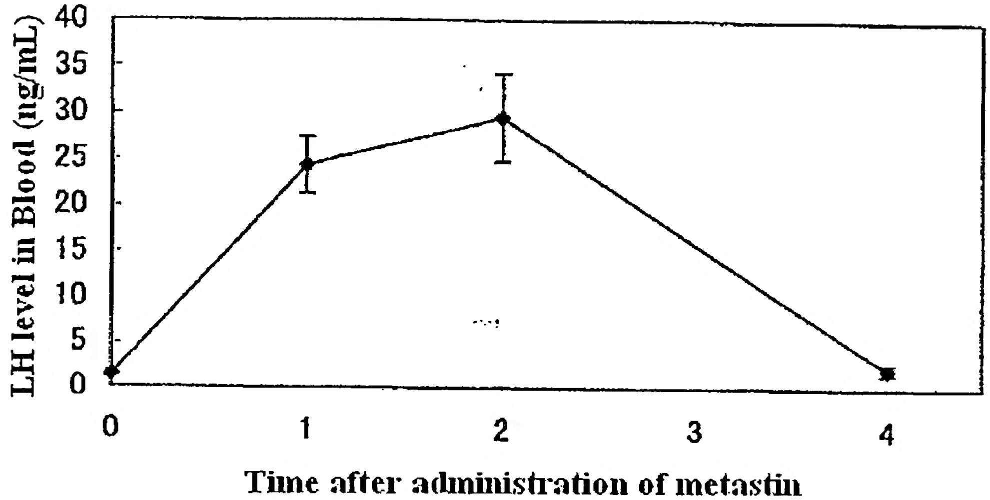

LH level in Blood (ng/mL)
40
35
30
25
20
15
10
5
0
0
1
2
3
4
Time after administration of metastin

FIG 16

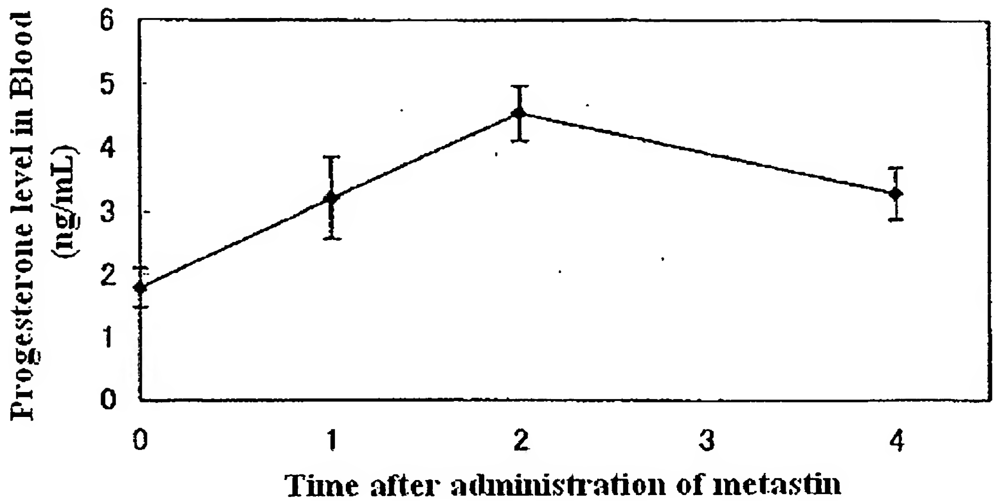

Progesterone level in Blood (ng/mL)
6
5
4
3
2
1
0
0
1
2
3
4
Time after administration of metastin

FIG 17

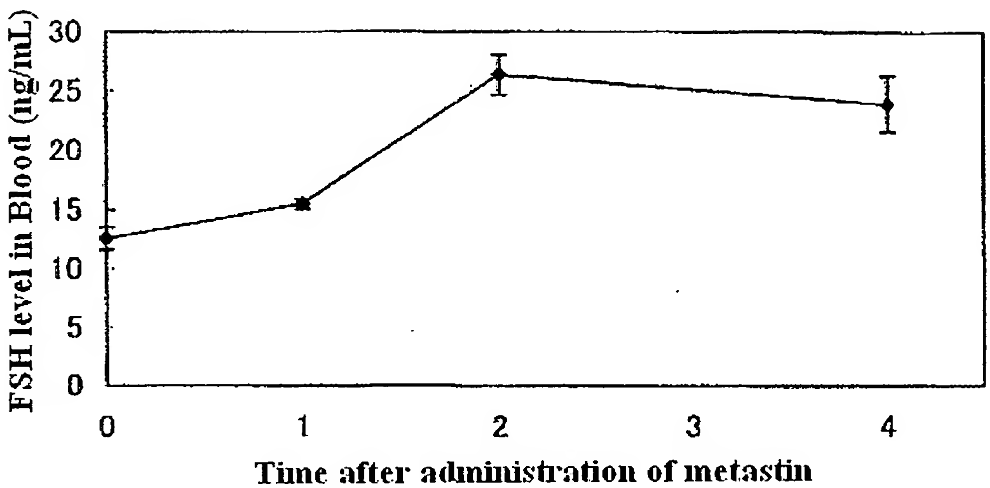

FSH level in Blood (ng/mL)
30
25
20
15
10
5
0
0
1
2
3
4
Time after administration of metastin

FIG 18

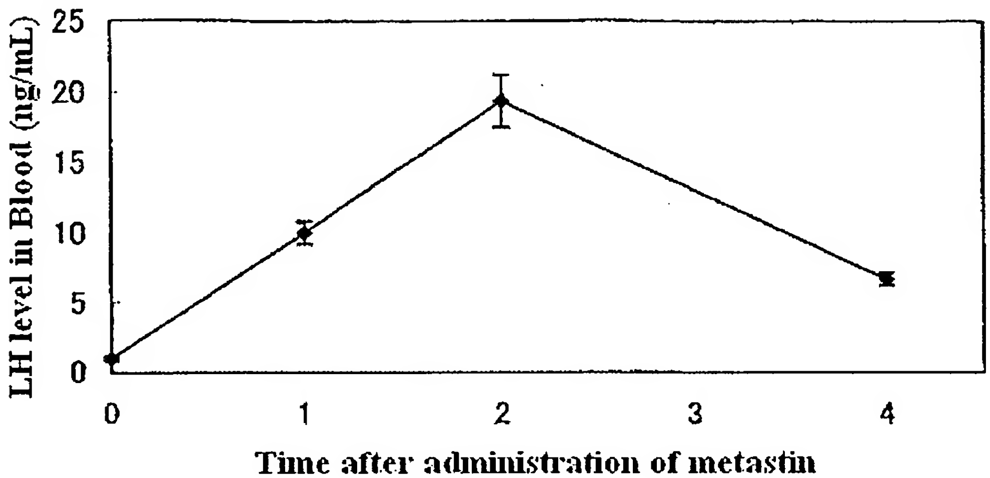

LH level in Blood (ng/mL)
25
20
15
10
5
0
0
1
2
3
4
Time after administration of metastin

FIG 19

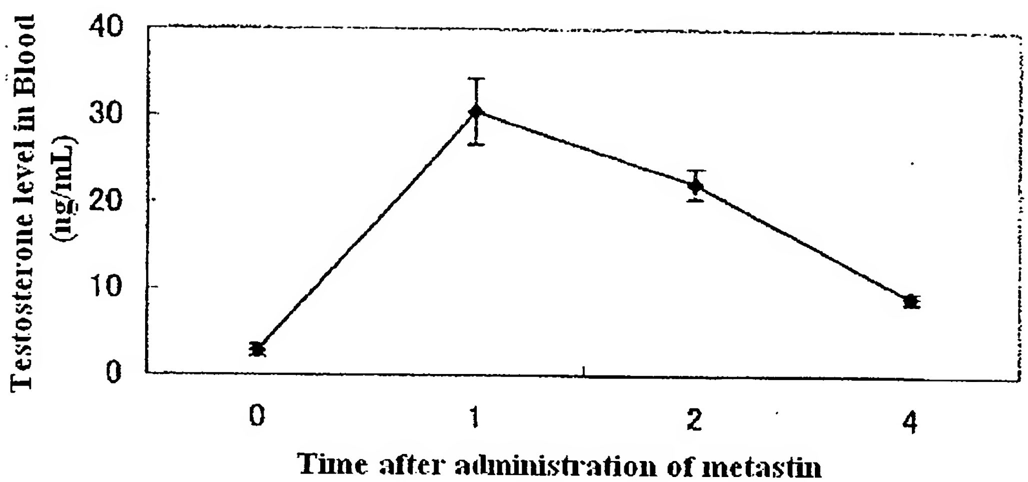

Testosterone level in Blood (ng/mL)
40
30
20
10
0
0
1
2
4
Time after administration of metastin

FIG 20

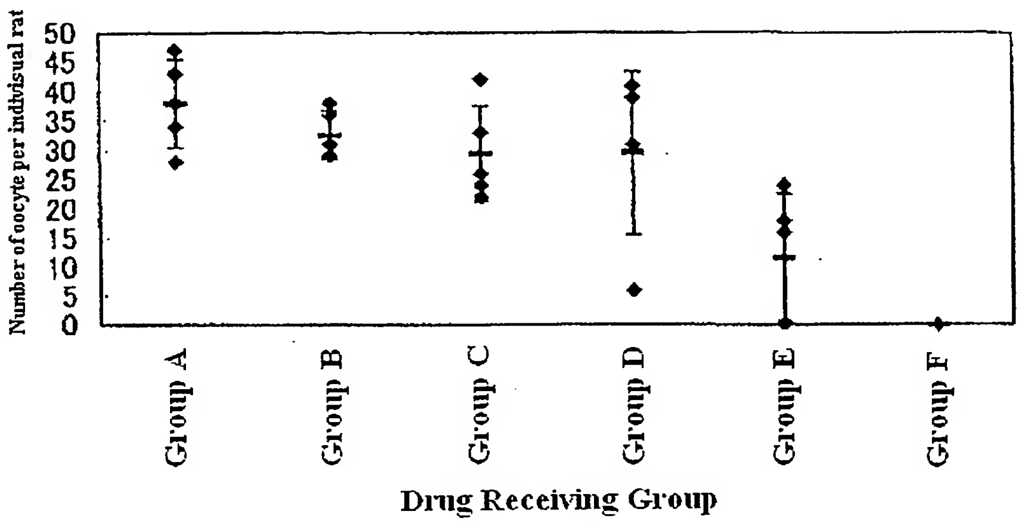

Number of oocyte per indivisual rat
50
45
40
35
30
25
20
15
10
5
0
Group A
Group B
Group C
Group D
Group E
Group F
Drug Receiving Group

FIG 21

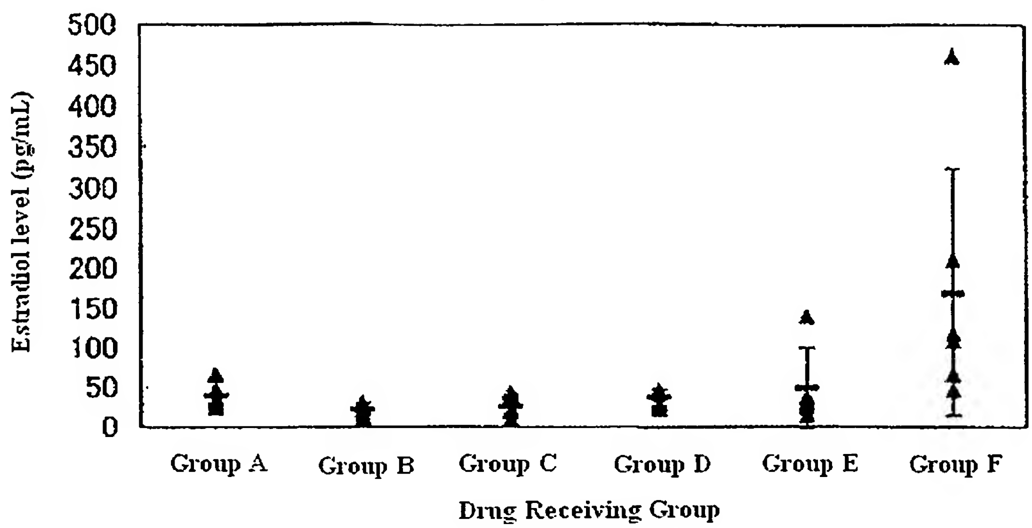
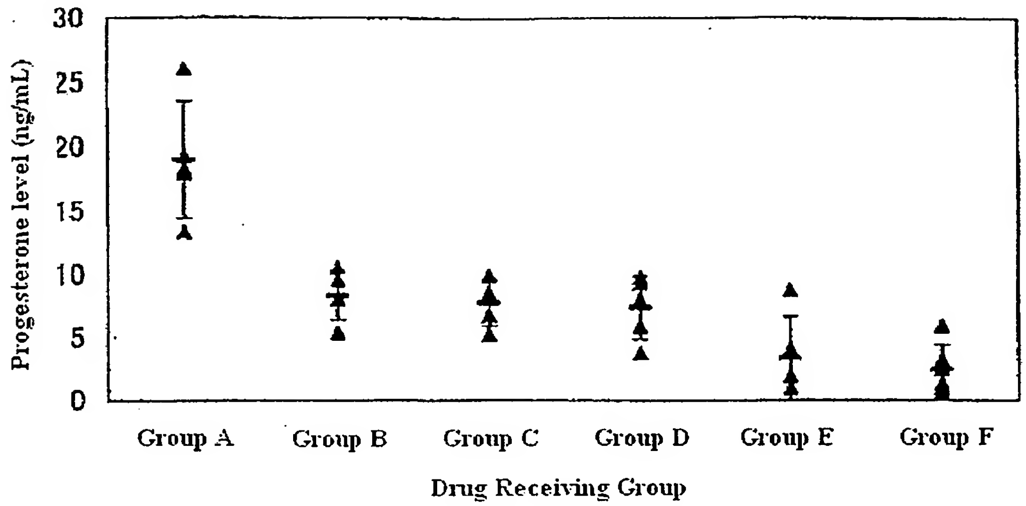

500
450
400
350
300
250
200
150
100
50
0
Estradiol level (pg/mL)
Group A
Group B
Group C
Group D
Group E
Group F
Drug Receiving Group

FIG 22


30
25
20
15
10
5
0
Progesterone level (ng/mL)
Group A
Group B
Group C
Group D
Group E
Group F
Drug Receiving Group

SEQUENCE LISTING

<110> Takeda Pharmaceutical Company, Ltd.

<120> Metastin Derivatives And Use Thereof

<130> PCT05-0008

<150> JP 2004-187671
<151> 2004-06-25

<160> 22

<210> 1
<211> 54
<212> PRT
<213> Homo sapiens

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1 5 10 15
Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly
20 25 30
Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn
35 40 45
Ser Phe Gly Leu Arg Phe
50

<210> 2
<211> 162
<212> DNA
<213> Homo sapiens

<400> 2
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gctccgcact ctcgtcagat cccggctccg cagggtgctg ttctggttca gcgtgaaaaa 120
gacctgccga actacaactg gaactctttc ggtctgcgtt tc 162

<210> 3
<211> 152
<212> PRT
<213> Mus musculus

<400> 3
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5 10 15
Glu Thr Val Asp Leu Pro Leu Pro Pro Arg Met Ile Ser Met Ala Ser
20 25 30
Trp Gln Leu Leu Leu Leu Leu Cys Val Ala Thr Tyr Gly Glu Pro Leu
35 40 45
Ala Lys Val Ala Pro Gly Ser Thr Gly Gln Gln Ser Gly Pro Gln Glu
50 55 60
Leu Val Asn Ala Trp Glu Lys Glu Ser Arg Tyr Ala Glu Ser Lys Pro
65 70 75 80
Gly Ser Ala Gly Leu Arg Ala Arg Arg Ser Ser Pro Cys Pro Pro Val
85 90 95
Glu Gly Pro Ala Gly Arg Gln Arg Pro Leu Cys Ala Ser Arg Ser Arg
100 105 110
Leu Ile Pro Ala Pro Arg Gly Ala Val Leu Val Gln Arg Glu Lys Asp
115 120 125
Leu Ser Thr Tyr Asn Trp Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg
130 135 140
Gln Ala Ala Arg Ala Ala Arg Gly
145 150

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<211> 456
<212> DNA
<213> Mus musculus

<400> 4
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ctgccccttc ctcccagaat gatctcaatg gcttcttggc agctgctgct tctcctctgt 120
gtcgccacct atggggagcc gctggcaaaa gtgaagcctg gatccacagg ccagcagtcc 180

ggaccccagg aactcgttaa tgcctgggaa aaggaatcgc ggtatgcaga gagcaagcct 240
gggtctgcag ggctgcgcgc tcgtaggtcg tcgccatgcc cgccggttga gggcccccgcg 300
gggcgccagc ggcccctgtg tgcctcccgc agtcgcctga tccctgcgcc ccgcggagcg 360
gtgctggtgc agcgggagaa ggacctgtcc acctacaact ggaactcctt cggcctgcgc 420
tacggcagga ggcaggcggc gcgggcagca cggggc 456

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<211> 156
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<213> Mus musculus

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5 10 15
Glu Thr Val Asp Leu Pro Leu Pro Pro Arg Met Ile Ser Met Ala Ser
20 25 30
Trp Gln Leu Leu Leu Leu Leu Cys Val Ala Thr Tyr Gly Glu Pro Leu
35 40 45
Ala Lys Val Ala Pro Leu Val Lys Pro Gly Ser Thr Gly Gln Gln Ser
50 55 60
Gly Pro Gln Glu Leu Val Asn Ala Trp Glu Lys Glu Ser Arg Tyr Ala
65 70 75 80
Glu Ser Lys Pro Gly Ser Ala Gly Leu Arg Ala Arg Arg Ser Ser Pro
85 90 95
Cys Pro Pro Val Glu Gly Pro Ala Gly Arg Gln Arg Pro Leu Cys Ala
100 105 110
Ser Arg Ser Arg Leu Ile Pro Ala Pro Arg Gly Ala Val Leu Val Gln
115 120 125
Arg Glu Lys Asp Leu Ser Thr Tyr Asn Trp Asn Ser Phe Gly Leu Arg
130 135 140
Tyr Gly Arg Arg Gln Ala Ala Arg Ala Ala Arg Gly
145 150 155

<210> 6
<211> 468
<212> DNA
<213> Mus musculus

<400> 6

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ctgccccttc ctcccagaat gatctcaatg gcttcttggc agctgctgct tctcctctgt 120
gtcgccacct atggggagcc gctggcaaaa gtggcacctt tggtgaagcc tggatccaca 180
ggccagcagt ccggacccca ggaactcgtt aatgcctggg aaaaggaatc gcggtatgca 240
gagagcaagc ctgggtctgc agggctgcgc gctcgtaggt cgtcgccatg cccgccggtt 300
gagggccccg cggggcgcca gcggccccctg tgtgcctccc gcagtcgcct gatccctgcg 360
ccccgcggag cggtgctggt gcagcgggag aaggacctgt ccacctacaa ctggaactcc 420
ttcggcctgc gctacggcag gaggcaggcg gcgcgggcag cacggggc 468

<210> 7
<211> 130
<212> PRT
<213> Rattus sp.

<400> 7

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5 10 15
Ser Phe Gly Glu Pro Leu Ala Lys Met Ala Pro Val Val Asn Pro Glu
20 25 30
Pro Thr Gly Gln Gln Ser Gly Pro Gln Glu Leu Val Asn Ala Trp Gln
35 40 45
Lys Gly Pro Arg Tyr Ala Glu Ser Lys Pro Gly Ala Ala Gly Leu Arg
50 55 60
Ala Arg Arg Thr Ser Pro Cys Pro Pro Val Glu Asn Pro Thr Gly His
65 70 75 80
Gln Arg Pro Pro Cys Ala Thr Arg Ser Arg Leu Ile Pro Ala Pro Arg
85 90 95
Gly Ser Val Leu Val Gln Arg Glu Lys Asp Met Ser Ala Tyr Asn Trp
100 105 110
Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg Gln Val Ala Arg Ala Ala
115 120 125
Arg Gly
130

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<211> 390
<212> DNA
<213> Rattus sp.

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caggaactcg ttaatgcctg gcaaaagggc ccgcggtatg cagagagcaa gcctggggct 180
gcaggactgc gcgctcgccg aacatcgcca tgcccgccgg tggagaaccc cacggggcac 240
cagcggcccc cgtgtgccac ccgcagtcgc ctgatccctg cgccccgcgg atcggtgctg 300
gtgcagcgcg agaaggacat gtcagcctac aactggaact cctttggcct gcgctacggc 360
aggaggcagg tggcgcgggc ggcacggggc 390

<210> 9
<211> 398
<212> PRT
<213> Homo sapiens

<400> 9
Met His Thr Val Ala Thr Ser Gly Pro Asn Ala Ser Trp Gly Ala Pro
5 10 15
Ala Asn Ala Ser Gly Cys Pro Gly Cys Gly Ala Asn Ala Ser Asp Gly
20 25 30
Pro Val Pro Ser Pro Arg Ala Val Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60
Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Gly Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140

Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160
Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Ala Tyr Cys Ser
180 185 190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220
Ala Ala Met Leu Arg His Leu Gly Arg Val Ala Val Arg Pro Ala Pro
225 230 235 240
Ala Asp Ser Ala Leu Gln Gly Gln Val Leu Ala Glu Arg Ala Gly Ala
245 250 255
Val Arg Ala Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu
275 280 285
Gly Pro Ala Gly Ser Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu
290 295 300
Lys Thr Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Arg Arg
325 330 335
Val Cys Pro Cys Ala Pro Arg Arg Pro Arg Arg Pro Arg Arg Pro Gly
340 345 350
Pro Ser Asp Pro Ala Ala Pro His Ala Glu Leu His Arg Leu Gly Ser
355 360 365
His Pro Ala Pro Ala Arg Ala Gln Lys Pro Gly Ser Ser Gly Leu Ala
370 375 380
Ala Arg Gly Leu Cys Val Leu Gly Glu Asp Asn Ala Pro Leu
385 390 395

<210> 10
<211> 1194
<212> DNA
<213> Homo sapiens

<400> 10

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ggctgcccgg gctgtggcgc caacgcctcg gacggcccag tcccttcgcc gcgggccgtg 120
gacgcctggc tcgtgccgct cttcttcgcg gcgctgatgc tgctgggcct ggtggggaac 180
tcgctggtca tctacgtcat ctgccgccac aagccgatgc ggaccgtgac caacttctac 240
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ctgctgtacc cgctgcccgg ctgggtgctg ggcgacttca tgtgcaagtt cgtcaactac 360
atccagcagg tctcggtgca ggccacgtgt gccactctga ccgccatgag tgtggaccgc 420
tggtacgtga cggtgttccc gttgcgcgcc ctgcaccgcc gcacgccccg cctggcgctg 480
gctgtcagcc tcagcatctg ggtaggctct gcggcggtgt ctgcgccggt gctcgccctg 540
caccgcctgt cacccgggcc gcgcgcctac tgcagtgagg ccttccccag ccgcgccctg 600
gagcgcgcct tcgcactgta caacctgctg gcgctgtacc tgctgccgct gctcgccacc 660
tgcgcctgct atgcggccat gctgcgccac ctgggccggg tcgccgtgcg ccccgcgccc 720
gccgatagcg ccctgcaggg gcaggtgctg gcagagcgcg caggcgccgt gcgggccaag 780
gtctcgcggc tggtggcggc cgtggtcctg ctcttcgccg cctgctgggg ccccatccag 840
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<210> 11
<211> 396
<212> PRT
<213> Rattus sp.

<400> 11

Met Ala Ala Glu Ala Thr Leu Gly Pro Asn Val Ser Trp Trp Ala Pro
5 10 15
Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Gly
20 25 30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
35 40 45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60

Phe Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr
65 70 75 80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Thr Trp Val Leu Gly Asp
100 105 110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160
Thr Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro His Thr Tyr Cys Ser
180 185 190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220
Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro
225 230 235 240
Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala
245 250 255
Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu
275 280 285
Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu
290 295 300
Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
305 310 315 320
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg
325 330 335
Val Cys Pro Cys Gly Pro Gln Arg Gln Arg Arg Pro His Ala Ser Ala
340 345 350
His Ser Asp Arg Ala Ala Pro His Ser Val Pro His Ser Arg Ala Ala

355 360 365

His Pro Val Arg Val Arg Thr Pro Glu Pro Gly Asn Pro Val Val Arg

370 375 380

Ser Pro Ser Val Gln Asp Glu His Thr Ala Pro Leu

385 390 395

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<211> 1188
<212> DNA
<213> Rattus sp.

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gatgcctggc tggtgcccct gtttttcgct gccctaatgt tgctggggct agtcgggaac 180
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<210> 13
<211> 396
<212> PRT
<213> Mus musculus

<400> 13

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Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Asp
20 25 30

Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
35 40 45

Phe Ala Thr Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
50 55 60

Tyr Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr
65 70 75 80

Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
85 90 95

Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Ala Trp Val Leu Gly Asp
100 105 110

Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
115 120 125

Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
130 135 140

Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145 150 155 160

Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
165 170 175

Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Thr Tyr Cys Ser
180 185 190

Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
195 200 205

Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
210 215 220

Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro
225 230 235 240

Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala
245 250 255

Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
260 265 270

Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu

275 280 285

Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Val

290 295 300

Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro

305 310 315 320

Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg

325 330 335

Val Cys Pro Cys Cys Arg Gln Arg Gln Arg Arg Pro His Thr Ser Ala

340 345 350

His Ser Asp Arg Ala Ala Thr His Thr Val Pro His Ser Arg Ala Ala

355 360 365

His Pro Val Arg Ile Arg Ser Pro Glu Pro Gly Asn Pro Val Val Arg

370 375 380

Ser Pro Cys Ala Gln Ser Glu Arg Thr Ala Ser Leu

385 390 395

<210> 14

<211> 1188

<212> DNA

<213> Mus musculus

<400> 14

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ggatgcccag gctgcggtgt caacgcctcg gatgacccag gctctgcgcc aaggccccctg 120

gatgcctggc tggttcccct gtttttcgct acactcatgt tgcttgggct ggtcggaaac 180

tcattggtca tctacgttat ctgccgccac aagcacatgc agacagttac caacttctac 240

atcgctaacc tggctgccac agacgtcact ttcctactgt gctgcgtgcc cttcaccgca 300

ctcctctacc cgctgcccgc ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360

atccagcagg tctcggtgca agccacatgt gccactctga cggccatgag tgtggaccgc 420

tggtatgtga ctgtgttccc gctgcgtgca cttcaccgcc gcactccgcg cctggccctg 480

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caccgcctgt cgccagggcc tcgcacctac tgcagcgagg cgtttcccag ccgcgccctg 600

gagcgcgcct tcgcgctcta caacctgctg gctctatatc tgctgccgct gctcgccacc 660

tgcgcctgct acggcgccat gctgcgccac ctgggccgtg cggctgtacg ccccgcaccc 720

actgacggcg ccctgcaggg acagctgcta gcacagcgcg ccggagcagt gcgcaccaag 780

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ctgttcctgg tgcttcaagc cctgggcccc tcgggggcct ggcaccctcg aagctatgcc 900

gcctacgcgg tcaagatctg ggctcactgc atgtcctaca gcaactcggc gctcaatccg 960
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<210> 15
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<212> PRT
<213> Artificial

<220>
<223> the C-terminus of the polypeptide is amide (-CONH2) form

<400> 15
Lys Asp Leu Pro Asn Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 10 15

<210> 16
<211> 10
<212> PRT
<213> Artificial

<220>
<223> the C-terminus of the polypeptide is amide (-CONH2) form

<400> 16
Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 10

<210> 17
<211> 9
<212> PRT
<213> Artificial

<220>
<223> the C-terminus of the polypeptide is amide (-CONH2) form

<400> 17
Asn Trp Asn Ser Phe Gly Leu Arg Phe
1 5 9

<210> 18
<211> 8
<212> PRT
<213> Artificial

<220>
<223> the C-terminus of the polypeptide is amide (-CONH2) form

<400> 18
Trp Asn Ser Phe Gly Leu Arg Phe
1 5 8

<210> 19
<211> 45
<212> DNA
<213> Homo sapiens

<400> 19
aaggacctgc cgaactacaa ctggaactcc ttcggcctgc gcttc 45

<210> 20
<211> 30
<212> DNA
<213> Homo sapiens

<400> 20
tacaactgga actccttcgg cctgcgcttc 30

<210> 21
<211> 27
<212> DNA
<213> Homo sapiens

<400> 21
aactggaact ccttcggcct gcgcttc 27

<210> 22
<211> 24
<212> DNA
<213> Homo sapiens

<400> 22
tggaactcct tcggcctgcg cttc 24